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For: CANNABINOID RECEPTOR MODULATOR

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[Document Name] Specification

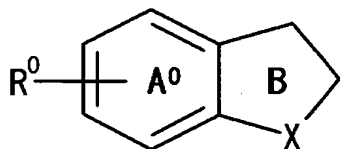
[Title of Invention] CANNABINOID RECEPTOR MODULATOR

[Claims]

[Claim 1]

5 A cannabinoid receptor modulator containing a compound represented by Formula (I₀)

[Chemical formula 1]

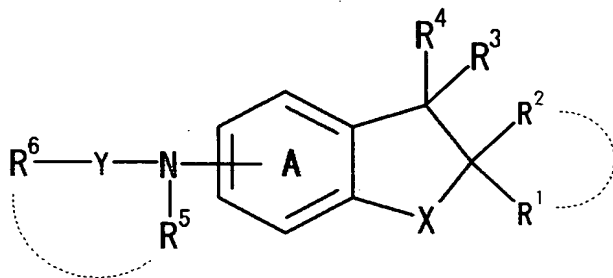


10 wherein, X is an oxygen atom, an optionally substituted sulfur atom or an optionally substituted nitrogen atom, R⁰ is an acylamino group, ring A⁰ is a benzene ring which may further have a substituent in addition to R⁰, and ring B is an optionally substituted 5-membered heterocycle, or a salt thereof or a prodrug thereof.

15 [Claim 2]

 The modulator as described in Claim 1 wherein the compound represented by Formula (I₀) or a salt thereof or a prodrug thereof is a compound represented by Formula (I)

[Chemical formula 2]



wherein, X is an oxygen atom, an optionally substituted sulfur atom or an optionally substituted nitrogen atom, R^1 , R^2 , R^3 and R^4 are independently a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxyl group, an optionally substituted mercapto group or an optionally substituted amino group, or R^2 and R^3 may be taken together to form a bond, or R^1 and R^2 may be taken with the adjacent carbon atom to form an optionally substituted ring, Y is $-CO-$, $-SO-$, or $-SO_2-$, R^5 is a hydrogen atom or an optionally substituted hydrocarbon group, R^6 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group or an optionally substituted amino group, or R^5 and R^6 may be taken with the adjacent carbon atom or sulfur atom and nitrogen atom to form an optionally substituted ring, and ring A is a benzene ring which may further have a substituent in addition to a group represented by the following formula

[Chemical formula 3]

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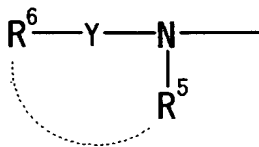
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wherein, each symbol has the same meaning as described above, or a salt thereof or a prodrug thereof.

[Claim 3]

5 The modulator as described in Claim 2 wherein R^1 and R^2 are a hydrogen atom, respectively.

[Claim 4]

The modulator as described in Claim 2 wherein R^1 and R^2 are a C_{1-4} alkyl group, respectively.

10 [Claim 5]

The modulator as described in Claim 2 wherein R^3 is a hydrogen atom.

[Claim 6]

15 The compound as described in Claim 2 wherein R^4 is an optionally substituted C_{6-14} aryl group or an optionally substituted 5 to 14-membered heterocyclic group.

[Claim 7]

The modulator as described in Claim 2 wherein R^5 is a hydrogen atom.

20 [Claim 8]

The modulator as described in Claim 2 wherein R^6 is an optionally substituted alkyl group or an optionally substituted amino group, and Y is $-\text{CO}-$.

[Claim 9]

The modulator as described in Claim 2 wherein R^1 , R^2 , R^3 and R^4 are independently a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted
5 heterocyclic group, an optionally substituted hydroxyl group, an optionally substituted mercapto group or an optionally substituted amino group.

[Claim 10]

The modulator as described in Claim 1 wherein X is an
10 oxygen atom.

[Claim 11]

The modulator as described in Claim 1 wherein 5-position of the fused-heterocycle in Formula (I₀) is substituted by R^0 .

15 [Claim 12]

The modulator as described in Claim 11 wherein 7-position of the fused-heterocycle in Formula (I₀) is further substituted by an optionally substituted C₆₋₁₄ aryl-C₁₋₄ alkyl group.

20 [Claim 13]

The modulator as described in Claim 1 wherein ring A^0 is a benzene ring which has further 1 to 3 C₁₋₆ alkyl group in addition to R^0 .

[Claim 14]

25 The modulator as described in Claim 1 wherein the

compound represented by Formula (I₀) or the salt thereof is a cannabinoid receptor agonist.

[Claim 15]

The modulator as described in Claim 14 wherein
5 cannabinoid receptor is type 1 cannabinoid receptor.

[Claim 16]

The modulator as described in Claim 1 wherein the compound represented by Formula (I₀) or the salt thereof is a cannabinoid receptor antagonist.

10 [Claim 17]

The modulator as described in Claim 16 wherein the cannabinoid receptor is type 1 cannabinoid receptor.

[Claim 18]

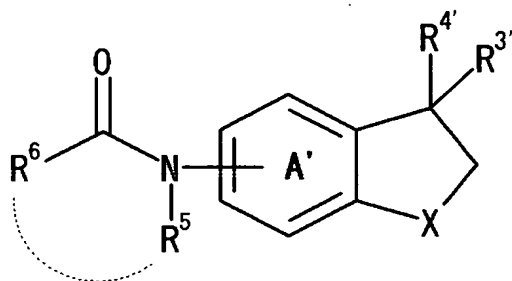
The modulator as described in Claim 1 which is an
15 agent for preventing or treating acute cerebrovascular disorders, spinal damage, head injury, multiple sclerosis, glaucoma or asthma.

[Claim 19]

The modulator as described in Claim 1 which is an
20 agent for preventing or treating memory disorders, psychiatric diseases or obesity.

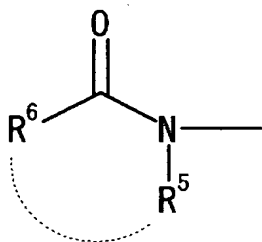
[Claim 20]

A compound represented by Formula (I')
[Chemical formula 4]



wherein, $R^{3'}$ is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted mercapto group or an optionally substituted amino group, $R^{4'}$ is an optionally substituted aryl group, or an optionally substituted heterocyclic group, ring A' is a benzene ring which may have further substituent in addition to a group represented by the following formula

10 [Chemical formula 5]



wherein, each symbol has the same meaning as described above,

and other symbols are as defined in claim 2, or a salt thereof.

15

[Claim 21]

The compound as described in Claim 20 wherein $R^{3'}$ is a hydrogen atom.

[Claim 22]

The compound as described in Claim 20 wherein $R^{4'}$ is an optionally substituted C_{6-14} aryl group or an optionally substituted 5 to 14-membered heterocyclic group.

5 [Claim 23]

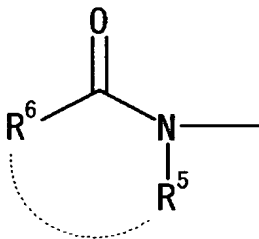
The compound as described in Claim 20 wherein $R^{4'}$ is an optionally substituted phenyl group.

[Claim 24]

10 The compound as described in Claim 20 wherein X is an oxygen atom.

[Claim 25]

The compound as described in Claim 20 wherein 5-position of the fused-heterocycle in Formula (I') is substituted by a group represented by the following formula
15 [Chemical formula 6]

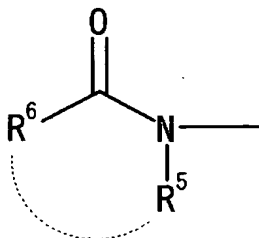


wherein, each symbol has the same meaning as described above.

[Claim 26]

20 The compound as described in Claim 20 wherein ring A is a benzene ring which has further 1 to 3 C_{1-6} alkyl group in addition to a group represented by the following formula

[Chemical formula 7]



wherein, each symbol has the same meaning as described above.

5 [Claim 27]

A prodrug of the compound as described in Claim 20.

[Claim 28]

A drug comprising the compound as described in Claim 20 or the prodrug as described in Claim 27.

10 [Claim 29]

A pharmaceutical composition comprising the compound as described in Claim 20 or the prodrug as described in Claim 27 and a pharmaceutically acceptable carrier.

[Detailed Description of the Invention]

15 [0001]

[Technical Field of the Invention]

The present invention relates to a benzene ring-fused 5-membered heterocyclic compound, especially a benzofuran derivative as a cannabinoid receptor modulator, and a pharmaceutical composition containing the same.

[0002]

[Prior Art]

Cannabinoid receptors belong to G-protein conjugated receptor having the seven transmembraneous domain. Among these, CB1 receptor is predominately distributed in the central nervous system, of which existence is known by
5 Devane W A et al. (Molecular Pharmacology, 34, 605-613 (1988)). CB2 receptor, which has a predominant cell distribution in the immune system and in the peripheral tissues, has been discovered by Munro S et al. (Nature, 365, 61-65 (1993)). CB1 receptor and CB2 receptor show 48% of
10 homology. 97 - 99% amino acid sequence of CB1 receptor is maintained in rat, mouse and human.

In the brain, CB1 receptor exists predominately in hippocampus, striatum, substantia nigra, basal forebrain area, olfactory bulb and cerebellum, and little in the
15 brain stem, medulla and thalamus. CB1 receptor is localized in the presynapse, and is considered to control inhibitably the release of neurotransmitters (Trends Pharmacological Sciences, 22, 565-572 (2001)). For CB1
20 receptor, four kinds of agonist are well known, i.e., classic cannabinoids of tetrahydrocannabinol (THC) derivatives which are dibenzopyran rings, non-classic cannabinoids which are bicyclic and tricyclic derivatives prepared by cleavage of the pyran rings of the THC
25 structure, aminoalkyl indols, and arachidonic acid derivatives such as anandamide which is known as an

endogenous agonist (Science, 258, 1946-1949 (1992)).

WIN55,212-2, a cannabinoid receptor agonist, has been reported to inhibit neural cell death based on cerebral ischemia (Journal of Neuroscience, 19, 2987-2995 (1999)).

5 The action is believed to be caused by inhibiting the release of glutamic acid through the activation of the CB1 receptor in the presynapse of glutamic acid neuron. Further, anandamide which is an endogenous ligand has been reported to show inhibitory action on neural cell death
10 after brain injury (Nature, 413, 527-531 (2001)). Further, Baker et al. have reported that WIN55,212-2, JWH-133, THC and methanandamide, which are cannabinoid receptor agonists, improved tremor or spasticity in the animal model of multiple sclerosis (Nature, 404, 84 (2000)).

15 Cerebrovascular disorders are the 2nd or 3rd leading cause of death in Japan, USA and Europe, and the 1st leading cause of serious aftereffect of diseases, incurring a big medical loss. At present, active treatment to resolve the etiology (tPA, etc.) is performed for some of
20 the patients suffering from cerebro-embolism and cerebro-thrombus, but it can be applied only to several percentages of the patients due to limited time-window for treatment. In most cases, only maintenance therapy of inhibiting cerebral edema and suppressing recurrence or enlargement
25 (thrombolytics) has been performed, but effective drugs for

treating the etiology or protecting the brain have not been developed. So far, many drugs having various mechanisms (e.g., glutamate antagonist, calcium antagonist, antioxidant, etc.) have been tried, but most of them have

5 failed in the clinical trials.

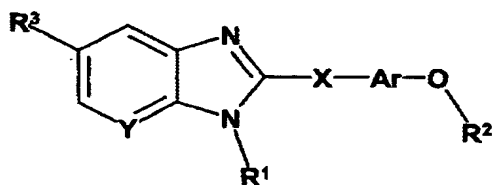
Clinical efficacy of the brain-hypothermia therapy as a brain protecting therapy, has been studied, with building up intensive care system for cerebral stroke. Brain-hypothermia therapy is a therapy that maintains the brain

10 temperature (cerebral temperature) low as 32 to 33°C, which has prominent brain-protecting effects. Therefore, this therapy has been drawing attention. However, this therapy requires 24-hour intensive care by intensive treatment facility and many staffs, which makes it difficult to be

15 accepted as a general therapy.

On the other hand, the following compounds have been reported as a compound which has an aminoacyl group on the benzene ring of a bicyclic heterocycle in which the benzene is fused with a 5-membered heterocycle.

20 1) A compound represented by the following Formula
[Chemical formula 8]

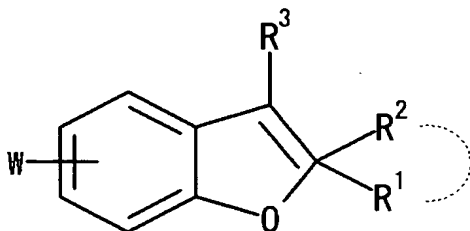


[wherein, R³ is an acylamino group, etc.] (Pamphlet of

WO02/085866) which has analgesic action.

2) A compound represented by the following Formula

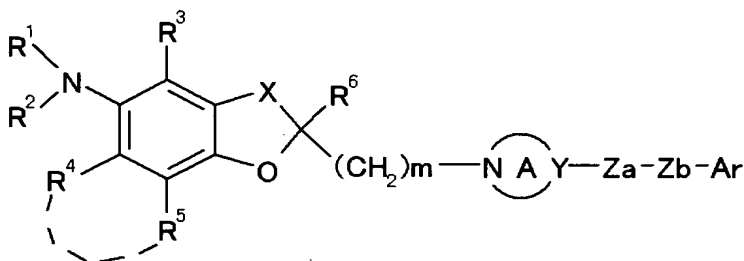
[Chemical formula 9]



5 [wherein, W is an acylamino group, etc.] which has proliferating and differentiating action on stem cells or precursor cells of neuron (JP-A-2002-348239).

3) A compound represented by the following Formula

[Chemical formula 10]



10

[wherein, the group NR^1R^2 is an aminoacyl group, etc.] which has sodium channel regulating action (Pamphlet of WO98/08842).

[Problems to be Solved by the Invention]

15

[0003]

Cerebrovascular disorders are broadly classified into cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage. For the treatment, a confirmation waiting time

for a proper diagnosis by X-ray, CT or MRI image diagnosis is required, which limits time-window for treatment.

However, a cannabinoid receptor agonist can resolve the problem of time-window for treatment since it is not

5 selective for a certain type of disease. Further, a cannabinoid receptor agonist is expected to be a useful agent of preventing, treating or diagnosing cerebrovascular disorders such as cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, etc., or head injury, or various
10 inflammatory diseases. In addition, it eliminates the need for heavy intensive care system by the intensive treatment facilities and staffs which are normally required in the hypothermia therapy, but is expected to exert equivalent brain protecting effects to the hypothermia therapy.

15 [0004]

Therefore, the object of the present invention is to provide a benzene ring-fused 5-membered heterocyclic compound, having modulating action on cannabinoid receptor function.

20 [0005]

[Means for Solving the Problems]

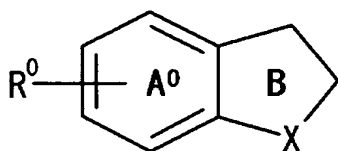
The present inventors have made extensive studies to solve above problems, and as results, have found unexpectedly that the compounds represented by Formula
25 (I₀), (I) and (I') which have an aminoacyl group on the

benzene-fused 5-membered heterocyclic group, have excellent modulating action on cannabinoid receptor function, to complete the present invention.

That is, the present invention provides:

- 5 (1) a cannabinoid receptor modulator containing a compound represented by Formula (I₀)

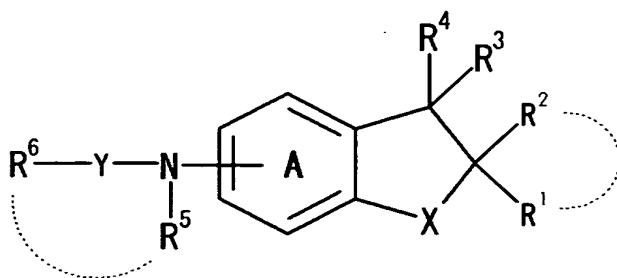
[Chemical formula 11]



- 10 wherein, X is an oxygen atom, an optionally substituted sulfur atom or an optionally substituted nitrogen atom, R⁰ is an acylamino group, ring A⁰ is a benzene ring which may further have a substituent in addition to R⁰, and ring B is an optionally substituted 5-membered heterocycle, or a salt thereof or a prodrug thereof;

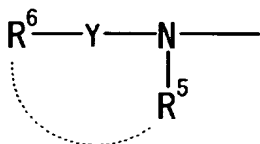
- 15 (2) the modulator as described in (1) wherein the compound represented by Formula (I₀) or a salt thereof or a prodrug thereof is a compound represented by Formula (I)

[Chemical formula 12]



wherein, X is an oxygen atom, an optionally substituted sulfur atom or an optionally substituted nitrogen atom, R^1 , R^2 , R^3 and R^4 are independently a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxyl group, an optionally substituted mercapto group or an optionally substituted amino group, or R^2 and R^3 may be taken together to form a bond, or R^1 and R^2 may be taken with the adjacent carbon atom to form an optionally substituted ring, Y is -CO-, -SO-, or -SO₂-, R^5 is a hydrogen atom or an optionally substituted hydrocarbon group, R^6 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group or an optionally substituted amino group, or R^5 and R^6 may be taken with the adjacent carbon atom or sulfur atom and nitrogen atom to form an optionally substituted ring, and ring A is a benzene ring which may further have a substituent in addition to a group represented by the following formula

[Chemical formula 13]



wherein, each symbol has the same meaning as described above, or a salt thereof or a prodrug thereof;

(3) the modulator as described in (2) wherein R^1 and R^2 are a hydrogen atom, respectively;

(4) the modulator as described in (2) wherein R^1 and R^2 are a C_{1-4} alkyl group, respectively;

5 (5) the modulator as described in (2) wherein R^3 is a hydrogen atom;

(6) the compound as described in (2) wherein R^4 is an optionally substituted C_{6-14} aryl group or an optionally substituted 5 to 14-membered heterocyclic group;

10 (7) the modulator as described in (2) wherein R^5 is a hydrogen atom;

(8) the modulator as described in (2) wherein R^6 is an optionally substituted alkyl group or an optionally substituted amino group, and Y is $-CO-$;

15 (9) the modulator as described in (2) wherein R^1 , R^2 , R^3 and R^4 are independently a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxyl group, an optionally substituted mercapto group or an
20 optionally substituted amino group;

(10) the modulator as described in (1) wherein X is an oxygen atom;

(11) the modulator as described in (1) wherein 5-position of the fused-heterocycle in Formula (I₀) is
25 substituted by R^0 ;

(12) the modulator as described in (11) wherein 7-position of the fused-heterocycle in Formula (I₀) is further substituted by an optionally substituted C₆₋₁₄ aryl-C₁₋₄ alkyl group;

5 (13) the modulator as described in (1) wherein ring A⁰ is a benzene ring which has further 1 to 3 C₁₋₆ alkyl group in addition to R⁰;

10 (14) the modulator as described in (1) wherein the compound represented by Formula (I₀) or the salt thereof is a cannabinoid receptor agonist;

 (15) the modulator as described in (14) wherein cannabinoid receptor is type 1 cannabinoid receptor;

15 (16) the modulator as described in (1) wherein the compound represented by Formula (I₀) or the salt thereof is a cannabinoid receptor antagonist;

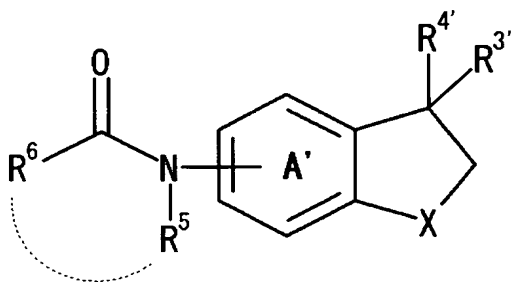
 (17) the modulator as described in (16) wherein the cannabinoid receptor is type 1 cannabinoid receptor;

20 (18) the modulator as described in (1) which is an agent for preventing or treating acute cerebrovascular disorders, spinal damage, head injury, multiple sclerosis, glaucoma or asthma;

 (19) the modulator as described in (1) which is an agent for preventing or treating memory disorders, psychiatric diseases or obesity;

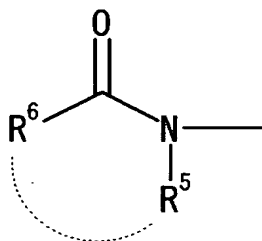
25 (20) a compound represented by Formula (I')

[Chemical formula 14]



wherein, $R^{3'}$ is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group,
 5 an optionally substituted mercapto group or an optionally substituted amino group, $R^{4'}$ is an optionally substituted aryl group, or an optionally substituted heterocyclic group, ring A' is a benzene ring which may have further substituent in addition to a group represented by the
 10 following formula

[Chemical formula 15]



wherein, each symbol has the same meaning as described above,
 15 and other symbols are as defined in (2), or a salt thereof;
 (21) the compound as described in (20) wherein $R^{3'}$ is a hydrogen atom;
 (22) the compound as described in (20) wherein $R^{4'}$ is

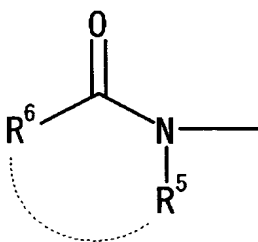
an optionally substituted C₆₋₁₄ aryl group or an optionally substituted 5 to 14-membered heterocyclic group;

(23) the compound as described in (20) wherein R^{4'} is an optionally substituted phenyl group;

5 (24) the compound as described in (20) wherein X is an oxygen atom;

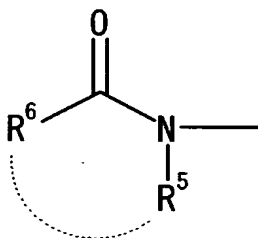
(25) the compound as described in (20) wherein 5-position of the fused-heterocycle in Formula (I') is substituted by a group represented by the following formula

10 [Chemical formula 16]



wherein, each symbol has the same meaning as described above;

(26) the compound as described in (20) wherein ring A is a benzene ring which has further 1 to 3 C₁₋₆ alkyl group in addition to a group represented by the following formula
15 [Chemical formula 17]



wherein, each symbol has the same meaning as described

above;

(27) a prodrug of the compound as described in (20);

(28) a drug comprising the compound as described in (20) or the prodrug as described in (27); and

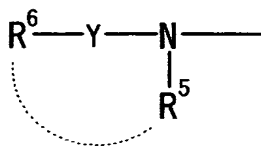
5 (29) a pharmaceutical composition comprising the compound as described in (20) or the prodrug as described in (27) and a pharmaceutically acceptable carrier; and the like.

[Mode for Carrying Out the Invention]

10 The compound represented by Formula (I₀) or a salt thereof [hereinafter, it may be abbreviated as Compound (I₀).] is preferably the compound represented by Formula (I) [hereinafter, it may be abbreviated as Compound (I).] or a salt thereof. The compound represented by Formula
15 (I') or a salt thereof which is contained in Compound (I₀) and Compound (I), is a novel compound [hereinafter, it may be abbreviated as Compound (I').].

[0006]

20 The acylamino group represented by R⁰ in the above-mentioned formulas is, for example, an acylamino group represented by the following formula



wherein, Y is -CO-, -SO-, or -SO₂-, R⁵ is a hydrogen atom

or an optionally substituted hydrocarbon group, R^6 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group or an optionally substituted amino group, or R^5 and R^6 may be taken with an adjacent carbon atom or a sulfur atom and a nitrogen atom to form an optionally substituted ring, etc.

As used herein, Y is preferably -CO-, R^5 is preferably a hydrogen atom, etc., and R^6 is preferably an optionally substituted hydrocarbon group or an optionally substituted amino group, etc.

[0007]

The hydrocarbon group of the "optionally substituted hydrocarbon group" represented by R^5 and R^6 includes, for example, a chain or cyclic hydrocarbon group (e.g., alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkandienyl, aryl, etc.), and the like. Among these, a C_{1-16} chain or cyclic hydrocarbon group, etc. are preferred. Among these, alkyl is preferred for R^6 .

The "alkyl" is preferably, for example, C_{1-10} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, 1-methylpropyl, n-hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 3,3-dimethylpropyl, 2-ethylbutyl, n-heptyl, 1-methylheptyl, 1-ethylhexyl, n-octyl, 1-methylheptyl, nonyl, etc.), or the

like. Among these, C_{1-6} alkyl is more preferred, and C_{1-4} alkyl is especially preferred for R^5 . On the other hand, C_{2-10} alkyl is more preferred, and C_{2-6} alkyl is especially preferred for R^6 .

5 The "alkenyl" is preferably, for example, C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, 2-methylallyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, etc.), or the like.

15 The "alkynyl" is preferably, for example, C_{2-6} alkynyl (e.g., ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, etc.), or the like.

 The "cycloalkyl" is preferably, for example, C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), or the like.

20 The "cycloalkenyl" is preferably, for example, C_{3-6} cycloalkenyl (e.g., 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 1-cyclobuten-1-yl, 1-cyclopenten-1-yl, etc.), or the like.

25 The "cycloalkandienyl" is preferably, for example, C_{5-6} cycloalkandienyl (e.g., 2,4-cyclopentandien-1-yl, 2,4-

cyclohexandien-1-yl, 2,5-cyclohexandien-1-yl, etc.), or the like.

The "aryl" is preferably, for example, C₆₋₁₄ aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenyl, anthryl, etc.),
 5 or the like.

[0008]

The "substituent" of the "optionally substituted hydrocarbon group" is preferably, for example, (1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine,
 10 etc.), (2) C₁₋₃ alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), (3) nitro, (4) cyano, (5) an optionally halogenated C₁₋₆ alkyl, (6) an optionally halogenated C₂₋₆ alkenyl, (7) an optionally halogenated C₂₋₆ alkynyl, (8) an optionally halogenated C₃₋₆ cycloalkyl,
 15 (9) C₆₋₁₄ aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenyl, anthryl, etc.), (10) an optionally halogenated C₁₋₆ alkoxy, (11) an optionally halogenated C₁₋₆ alkylthio or mercapto, (12) hydroxy, (13) amino, (14) mono-C₁₋₆ alkylamino (e.g., methylamino, ethylamino, etc.), (15)
 20 mono-C₆₋₁₄ arylamino (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.), (16) di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino, etc.), (17) di-C₆₋₁₄ arylamino (e.g., diphenylamino, etc.), (18) acyl, (19) acylamino, (20) acyloxy, (21) an optionally substituted 5- to 7-
 25 membered saturated cyclic amino, (22) a 5- to 10-membered

aromatic heterocyclic group (e.g., 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, etc.), (23) sulfo, (24)
 5 C₆₋₁₄ aryloxy (e.g., phenyloxy, naphthyloxy, etc.) or (25) oxo, etc.

The "hydrocarbon group" may have, for example, the 1 to 5, preferably 1 to 3 above-mentioned substituents at any substitutable position, and if the number of substituent is
 10 two or more, each substituent is the same or different.

[0009]

The above-mentioned "optionally halogenated C₁₋₆ alkyl" is, for example, C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl,
 15 hexyl, etc.) which may be substituted with 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), etc. Specific examples are methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl,
 20 butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.

The above-mentioned "optionally halogenated C₂₋₆ alkenyl" is, for example, C₂₋₆ alkenyl (e.g., vinyl, allyl,
 25

isopropenyl, butenyl, isobutenyl, sec-butenyl, etc.) which may be substituted with 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), or the like. Specific examples are vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, 3,3,3-trifluoro-1-propenyl, 4,4,4-trifluoro-1-butenyl, etc.

The above-mentioned "optionally halogenated C₂₋₆ alkynyl" is, for example, C₂₋₆ alkynyl (e.g., ethynyl, propargyl, butynyl, 1-hexynyl, etc.) which may be substituted with 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), or the like. Specific examples are ethynyl, propargyl, butynyl, 1-hexynyl, 3,3,3-trifluoro-1-propynyl, 4,4,4-trifluoro-1-butyne, etc.

The above-mentioned "optionally halogenated C₃₋₆ cycloalkyl" is, for example, C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) which may be substituted with 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), or the like. Specific examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl, etc.

The above-mentioned "optionally halogenated C₁₋₆ alkoxy" is, for example, C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy,

pentyloxy, hexyloxy, etc.) which may be substituted with 1
 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine,
 chlorine, bromine, iodine, etc.), etc. Specific examples
 are methoxy, difluoromethoxy, trifluoromethoxy, ethoxy,
 5 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-
 trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy,
 etc.

The above-mentioned "optionally halogenated C₁₋₆
 alkylthio" is, for example, C₁₋₆ alkylthio (e.g., methylthio,
 10 ethylthio, propylthio, isopropylthio, butylthio, sec-
 butylthio, tert-butylthio, etc.) which may be substituted
 with 1 to 5, preferably 1 to 3 halogen atoms (e.g.,
 fluorine, chlorine, bromine, iodine, etc.), or the like.
 Specific examples are methylthio, difluoromethylthio,
 15 trifluoromethylthio, ethylthio, propylthio, isopropylthio,
 butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio,
 etc.

[0010]

The above-mentioned "acyl" is, for example, formyl,
 20 carboxyl, carbamoyl, C₁₋₆ alkyl-carbonyl (e.g., acetyl,
 propionyl, etc.), C₃₋₆ cycloalkyl-carbonyl (e.g.,
 cyclopropylcarbonyl, cyclopentylcarbonyl,
 cyclohexylcarbonyl, etc.), C₁₋₆ alkoxy-carbonyl (e.g.,
 methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-
 25 butoxycarbonyl, etc.), C₆₋₁₄ aryl-carbonyl (e.g., benzoyl,

1-naphthoyl, 2-naphthoyl, etc.), C₇₋₁₆ aralkyl-carbonyl (e.g., phenylacetyl, phenylpropionyl, etc.), C₆₋₁₄ aryloxy-carbonyl (e.g., phenoxycarbonyl, etc.), C₇₋₁₆ aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), 5- or 6-membered heterocyclic carbonyl (e.g., nicotinoyl, isonicotinoyl, 2-tenoyl, 3-tenoyl, 2-furoyl, 3-furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperidinocarbonyl, 1-pyrrolidinylcarbonyl, etc.), mono-C₁₋₆ alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C₁₋₆ alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C₆₋₁₄ aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.), C₁₋₆ alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.), C₆₋₁₄ arylsulfonyl (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl, etc.), C₁₋₆ alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, etc.), C₆₋₁₄ arylsulfinyl (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl, etc.), or the like.

The above-mentioned "acylamino" is, for example, formylamino, C₁₋₆ alkyl-carbonylamino (e.g., acetylamino, etc.), C₆₋₁₄ aryl-carbonylamino (e.g., phenylcarbonylamino,

naphthylcarbonylamino, etc.), C₁₋₆ alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, etc.), C₁₋₆ alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), C₆₋₁₄ arylsulfonylamino (e.g., phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino, etc.), or the like.

The above-mentioned "acyloxy" is, for example, C₁₋₆ alkyl-carbonyloxy (e.g., acetoxy, propionyloxy, etc.), C₆₋₁₄ aryl-carbonyloxy (e.g., benzoyloxy, naphthylcarbonyloxy, etc.), C₁₋₆ alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C₁₋₆ alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C₁₋₆ alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C₆₋₁₄ aryl-carbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), nicotinoyloxy, etc.

The "5- to 7-membered saturated cyclic amino" of the above-mentioned "optionally substituted 5- to 7-membered saturated cyclic amino" is, for example, morpholino, thiomorpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, etc. The "substituent" of the "optionally substituted 5- to 7-membered saturated cyclic amino" is, for example, C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl,

isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), C₆₋₁₄ aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl, etc.), 5- to 10-membered aromatic heterocyclic group (e.g., 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, etc.), or the like. The "5- to 7-membered saturated cyclic amino" may have 1 to 3 substituents.

[0011]

10 The substituent in the "optionally substituted hydroxyl group" and the "optionally substituted amino group" represented by R⁶ is, for example, one as defined in the substituent of the "optionally substituted hydrocarbon group" represented by R⁵ and R⁶. The "amino group" may have 1 to 2 substituents.

[0012]

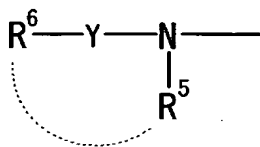
20 The "ring" that R⁵ and R⁶ may be taken with the adjacent carbon atom and the nitrogen atom to form is, for example, a 5- to 7-membered saturated or non-saturated nitrogen-containing heterocycle which may contain 1 to 2 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, etc. as a ring-constituting atom in addition to nitrogen atom (e.g., pyrrolidin-2-one, thiazolidin-2-one, thiazolidin-4-one, oxazolidin-2-one, 25 oxazolidin-4-one, imidazolidin-2-one, imidazolidin-4-one,

piperidin-2-one, thiazinan-4-one, thiomorpholin-3-one, azepan-2-one, dihydropyrrol-2-one, dihydropyridine-2-one, pyridine-2-one, tetrahydroazepin-2-one, dihydroazepin-2-one, etc.), or the like. The heteroatom in the "nitrogen-
 5 containing heterocycle" is preferably 1 to 2 kinds. This "ring" may have further substituent in addition to oxo group. The "substituent" is, for example, one as defined in the substituent of the "optionally substituted hydrocarbon group" represented by R^5 and R^6 . The number of
 10 the "substituent" is, for example, 1 to 5 (preferably 1 to 3, more preferably is 1 to 2).

[0013]

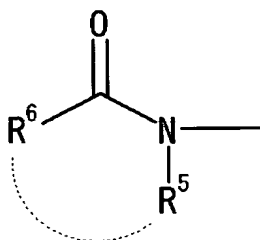
The substituent that ring A^0 in the above-mentioned formulas may further have in addition to R^0 , the
 15 substituent that ring A in the above-mentioned formulas may further have in addition to a group represented by the following formula

[Chemical formula 19]



20 wherein, each symbol has the same meaning as described above, and the substituent that ring A' in the above-mentioned formulas may further have in addition to a group represented by the following formula

[Chemical formula 20]



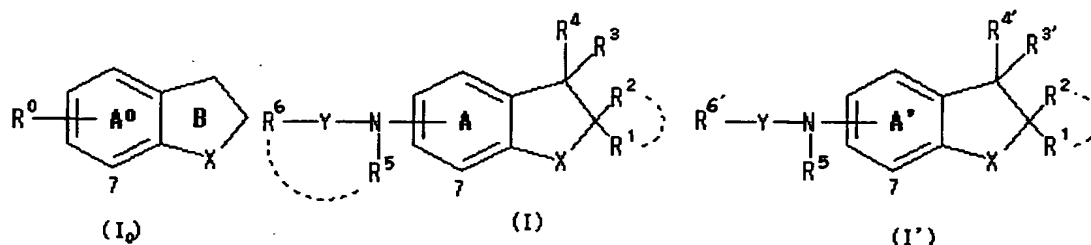
wherein, each symbol has the same meaning as described above (hereinafter, these may be referred to simply as the
 5 substituent that ring A, etc. may further have) are, for example, an "optionally substituted hydrocarbon group", an "optionally substituted hydroxyl group", and an "optionally substituted amino group". The "optionally substituted hydrocarbon group", the "optionally substituted hydroxyl
 10 group" and the "optionally substituted amino group" are, for example, one as defined in the "optionally substituted hydrocarbon group", the "optionally substituted hydroxyl group" and the "optionally substituted amino group", respectively represented by R^6 .

15 Among these, the substituent that ring A, etc. may further have, is preferably an optionally substituted alkyl group, hydroxyl group and amino group. As the alkyl group of the "optionally substituted alkyl group", preferred is a C_{1-6} alkyl group (e.g., methyl, ethyl, propyl,
 20 isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.).

Especially, when 7-position (in the following formula,

represented by number 7.) of the fused-heterocycle in Formula (I₀), Formula (I) and Formula (I') is substituted by the substituent, an optionally substituted C₆₋₁₄ aryl-C₁₋₆ alkyl group is also preferred. The "C₆₋₁₄ aryl-C₁₋₆ alkyl group" of the "optionally substituted C₆₋₁₄ aryl-C₁₋₆ alkyl group" is, for example, benzyl, α-methylbenzyl, etc., and the substituent thereof is, for example, one as defined in the substituent of the "optionally substituted hydrocarbon group" represented by R⁶.

[Chemical formula 21]



The number of the "substituent" that ring A, etc. may further have is, for example, 1 to 3 (preferably 2 to 3). When the number of the "substituent" is 2 or more, preferably, all of the substituents are an optionally substituted alkyl group, or at least one of the substituents is an optionally substituted alkyl group and the rest is a hydroxyl group or an amino group.

[0014]

The substituent of the "optionally substituted 5-membered heterocycle" represented by ring B in the above-

mentioned formulas is, for example, an "optionally substituted hydrocarbon group", an "optionally substituted hydroxyl group", an "optionally substituted amino group", an "optionally substituted heterocyclic group", and an
5 "optionally substituted mercapto group". Ring B may have 1 to 5 (preferably 2 to 4) of these substituents. When ring B is unsubstituted, ring A, ring A₀, and ring A' are preferably substituted with the above-mentioned "optionally substituted C₆₋₁₄ aryl-C₁₋₆ alkyl group" at 7-position of the
10 fused-heterocycle in Formula (I₀), Formula (I) and Formula (I'), respectively.

The "optionally substituted hydrocarbon group", the "optionally substituted hydroxyl group", and the "optionally substituted amino group" are, for example, ones
15 as defined in the "optionally substituted hydrocarbon group", the "optionally substituted hydroxyl group", and the "optionally substituted amino group" represented by R⁶, respectively.

The "heterocyclic group" of the "optionally substituted heterocyclic group" is preferably a 5- to 14-membered heterocyclic group. The 5- to 14-membered heterocyclic group is, for example, a 5- to 14-membered heterocyclic group (aromatic heterocyclic group, saturated or unsaturated non-aromatic heterocyclic group) containing
20 at least 1 (preferably 1 to 4) of one to three kinds of
25

heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in addition to carbon atom, etc.

The "aromatic heterocyclic group" is, for example, a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group containing one or more (for example, 1 to 4) heteroatoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to a carbon atom, etc. Specific examples are aromatic heterocycle such as thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, isoindolidine, xanthrene, phenoxathine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthiridine, quinoxaline, quinazoline, cinnoline, carbazole, β -carboline, phenanthridine, acrydine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isoxazole, furazane, phenoxazine, etc., or a group obtained by subtracting any one hydrogen atom from a ring which is formed by fusion of these ring(s) (preferably, monocyclic ring) with one or more (preferably 1 or 2) aromatic rings (e.g., benzene ring, etc.), or the like. The examples include 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, 2- or

3-thienyl, etc.

The "non-aromatic heterocyclic group" is, for example, a 3 to 8-membered (preferably 5- or 6-membered) saturated or unsaturated non-aromatic heterocyclic group such as
5 oxiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, etc.

The substituent of the "optionally substituted heterocyclic group" is, for example, one as defined in the
10 substituent of the "optionally substituted hydrocarbon group" represented by R^5 and R^6 .

The substituent of the "optionally substituted mercapto group" is, for example, one as defined in the substituent of the "optionally substituted hydrocarbon
15 group" represented by R^5 and R^6 .

These optional substituents may be substituted in the number of 1 to 5 (preferably 1 to 4, further preferably 1 to 2) at any substitutable position.

Or these substituents may be combined together to form
20 a ring or a bond. That is, the 5-membered heterocycle of the "optionally substituted heterocycle" represented by ring B may be saturated or unsaturated, and examples thereof include dihydropyrrole, ethene, pyrrole, dihydrothiophene, thiophene, dihydrofuran, furan and the
25 like.

[0015]

The "optionally substituted hydrocarbon group", the "optionally substituted heterocyclic group", the "optionally substituted hydroxyl group", the "optionally substituted mercapto group" and the "optionally substituted amino group" represented by R^1 , R^2 , R^3 , $R^{3'}$ and R^4 in the above-mentioned formulas are, for example, ones as defined in the substituent of the "optionally substituted 5-membered heterocycle" represented by ring B.

Among these, a hydrogen atom, a C_{1-4} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.), or the like are preferred respectively for R^1 , R^2 , R^3 , and $R^{3'}$. A hydrogen atom, etc. are further preferred for R^3 and R^{3a} .

In addition, among these, an optionally substituted aryl group, and an optionally substituted heterocyclic group, etc. are preferred for R^4 .

The "aryl group" of the "optionally substituted aryl group" (and the "optionally substituted aryl group" represented by $R^{4'}$) is, for example, C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenyl, anthryl, etc.), or the like. The substituent of the "optionally substituted aryl group" is, for example, one as defined in the "substituent" of the "optionally substituted hydrocarbon group" which is a substituent of the "optionally

substituted 5-membered heterocycle" represented by ring B.

The heterocyclic group of the "optionally substituted heterocyclic group" (and the "optionally substituted heterocyclic group" represented by $R^{4'}$) is, for example, one as defined in the "optionally substituted heterocyclic group" as substituent of the "optionally substituted 5-membered heterocycle" represented by ring B.

[0016]

The ring of the "optionally substituted ring" that R^1 and R^2 may be taken with the adjacent carbon atom to form is, for example, a 3- to 8-membered homo- or heterocycle. The "3- to 8-membered homocycle" is, for example, C_{3-8} cycloalkane, etc.

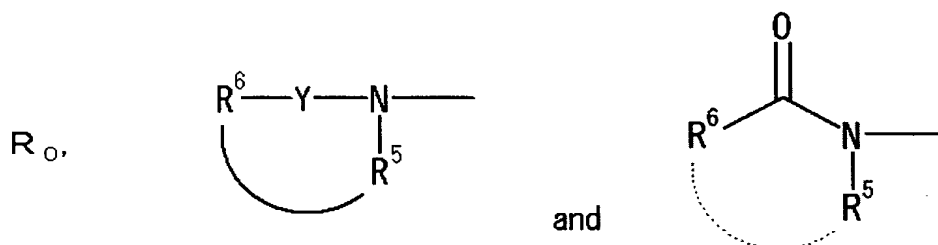
The "3- to 8-membered heterocycle" is, for example, a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in addition to carbon atom (e.g., aziridine, azetidine, morpholine, thiomorpholine, piperazine, piperidine, pyrrolidine, hexamethyleneimine, heptamethyleneimine, hexahydropyrimidine, etc.).

The "substituent" of the "optionally substituted ring" that R^1 and R^2 may form with the adjacent carbon atom is, for example, one as defined in the "substituent" of the "optionally substituted hydrocarbon group" represented by the above-mentioned R^5 and R^6 , of the same number.

[0017]

The 5-positions of the fused-heterocycle in Formula (I₀), Formula (I) and Formula (I'), are preferably substituted by a group represented by

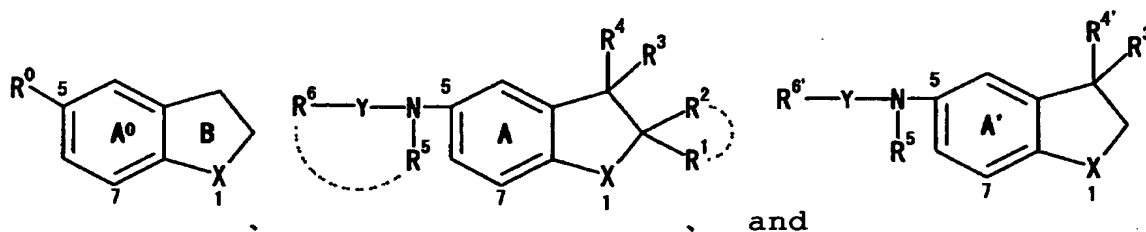
5 [Chemical formula 22]



wherein, each symbol has the same meaning as described above, respectively. In other words, the compounds represented by Formula (I₀), Formula (I) and Formula (I'), respectively are preferably,

10

[Chemical formula 23]



wherein, numbers around the rings indicate position number, respectively.

15

[0018]

Salts of the compounds represented by Formula (I₀), Formula (I), and Formula (I') (hereinafter, they may be abbreviated as Compound (I), etc.) include salts, when Compound (I) has an acidic group such as a carboxyl group,

with an inorganic base (e.g., alkali metals such as sodium and potassium and alkaline earth metals such as calcium and magnesium, transitional metals such as zinc, iron and copper, etc.) or with an organic base (e.g., organic amines
5 such as trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine, and basic amino acids such as arginine, lysine, ornithine, etc.), or the like.

10 On the other hand, when Compound (I), etc. have a basic group such as an amino group, etc., such salts include salts with inorganic acids and organic acids (e.g., hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, carbonic acid, bicarbonic acid, formic acid, acetic
15 acid, propionic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.), and acidic amino acids such as asparaginic acid, glutamic acid,
20 etc.

The prodrug of Compound (I), etc. means a compound which is converted to Compound (I), etc. by a reaction with an enzyme, an gastric acid, etc. under the physiological condition in vivo, that is, by enzymatic oxidation,
25 reduction, hydrolysis, etc.; or by hydrolysis with gastric

acid, etc. Examples of the prodrug of Compound (I), etc. include a compound wherein the amino group of Compound (I), etc. is acylated, alkylated or phosphorylated (e.g., a compound wherein the amino group of Compound (I), etc. is eicosanylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated or tert-butylated); a compound wherein the hydroxyl group of Compound (I), etc. is acylated, alkylated, phosphorylated or converted into borate (e.g., a compound wherein the hydroxyl group of Compound (I), etc. is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated or dimethylaminomethylcarbonylated); a compound wherein a carboxyl group of Compound (I), etc. is esterified or amidated (e.g., a compound wherein a carboxyl group of Compound (I), etc. is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, cyclohexyloxycarbonylethyl esterified, methylamidated, etc.); etc. These prodrugs can be produced by per se known methods from Compound (I), etc.

In addition, the prodrug of Compound (I), etc. may be

a compound which is converted into Compound (I), etc. under the physiological conditions as described in "Pharmaceutical Research and Development", Vol. 7 (Drug Design), pp. 163-198 published in 1990 by Hirokawa Publishing Co.

[0019]

Hereinafter, the methods for producing Compound (I), etc. of the present invention will be explained.

Compound (I), etc. of the present invention can be produced by the methods below or analogous methods thereto.

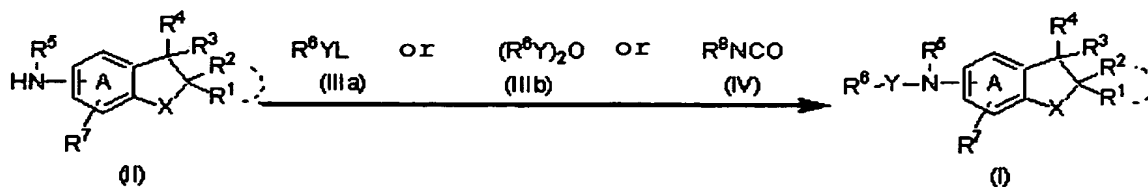
In the following Reaction Schemes, each symbol of the compounds has the same meaning unless otherwise stated. The compounds in Reaction Scheme include salts thereof, and the salts are, for example, ones as defined in Compound (I), etc.

[0020]

Compound (I) can be produced by a method described in the following Reaction Scheme 1.

Reaction Scheme 1

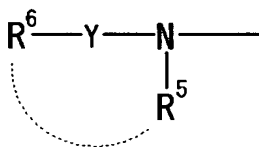
[Chemical formula 24]



In the Reaction Scheme 1, L is a leaving group, R⁷ is

a substituent that ring A may further have in addition to a group represented by the following formula

[Chemical formula 25]



wherein, each symbol has the same meaning as described above, or a corresponding group thereto, R^8 is a group formed by subtracting a $>\text{NH}$ group from an optionally substituted amino group represented by R^6 , and other symbols have the same meanings as defined above.

Compound (I) can be produced by reacting Compound (II) with Compound (IIIa), Compound (IIIb) or Compound (IV), if desired, under the presence of base or acid.

Compound (IIIa), Compound (IIIb) or Compound (IV) is commercially available, and further can be produced by per se known methods or analogous methods thereto.

The "leaving group" represented by L is, for example, hydroxy, a halogen atom (for example, fluorine, chlorine, bromine, iodine, etc.), optionally halogenated C_{1-5} alkylsulfonyloxy (e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, etc.), optionally substituted C_{6-10} arylsulfonyloxy, optionally substituted phenyl group, optionally substituted 2-thiobenzothiazole, etc.

Compound (IIIa), Compound (IIIb) or Compound (IV) is used in an amount of about 1.0 to 10 moles, preferably about 1.0 to 2.0 moles, relative to 1 mole of Compound (II).

The "base" is, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, etc., aromatic amines such as pyridine, lutidine, etc., tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc., alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc., metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc., or the like.

The "acid" is, for example, methanesulfonic acid, p-toluenesulfonic acid, camphor-sulfonic acid, etc.

The "base" is used in an amount of about 0.1 to 10 equivalents, preferably 0.8 to 2 equivalents, relative to Compound (II).

The "acid" is used in an amount of about 0.1 to 10 equivalents, preferably 0.8 to 3 equivalents, relative to Compound (II).

The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction.

Such solvents are not particularly limited if the reaction proceeds, and include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., nitrogen-containing aromatic hydrocarbons such as pyridine, lutidine, quinoline, etc. or mixed solvent thereof. The reaction temperature is about -40 to 150°C, preferably 0 to 100°C. The reaction time is usually 5 minutes to 24 hours, preferably 10 minutes to 5 hours.

Thus obtained product (I) may be isolated from the reaction mixture by a conventional method, and easily purified by conventional means of separation such as recrystallization, distillation, chromatography, etc.

Alternatively, Compound (II) and Compound (IIIa) may be reacted under the presence of a suitable condensing agent.

Compound (IIIa) is used in an amount of about 0.8 to about 10.0 moles, preferably about 0.8 to about 2.0 moles, relative to 1 mole of Compound (II).

The "condensing agent" is, for example, N,N'-

dicarbodiimides such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) hydrochloride, etc., azolides such as N,N'-carbonylimidazole, etc., a dehydrating agent such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, diethyl cyanophosphate, phosphorus oxychloride, acetic anhydride, etc., a 2-halogenopyridinium salt such as 2-chloromethylpyridinium iodide, 2-fluoro-1-chloromethylpyridinium iodide, etc.

10 The condensing agent is used in an amount of about 0.8 to about 5.0 moles, preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (II).

 In addition, if desired, the reaction may be conducted under the coexistence of base with the condensing agent.

15 The "base" is, for example, basic salts such as potassium acetate, sodium acetate, etc., tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine,

20 etc., or 1-hydroxy-1H-benzotriazole (HOBt) monohydrates, etc. The base is used in an amount of about 0.5 to about 5.0 moles, preferably about 2.0 to about 3.0 moles, relative to 1 mole of Compound (II).

 The present reaction is advantageously carried out

25 using an inert solvent. Such solvents are, for example,

alcohols such as methanol, ethanol, propanol, etc., hydrocarbons such as hexane, cyclohexane, benzene, toluene, xylene, etc., ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.,
5 amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc., sulfoxides such as dimethylsulfoxide, etc., halogenated carbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., nitriles such as acetonitrile,
10 propionitrile, etc., acid anhydrides such as acetic anhydride, etc., or a mixed solvent thereof, or the like.

The reaction time is usually about 10 minutes to about 48 hours, preferably about 30 minutes to about 24 hours. The reaction temperature is usually about -20 to about
15 150°C, preferably about 0 to about 100°C.

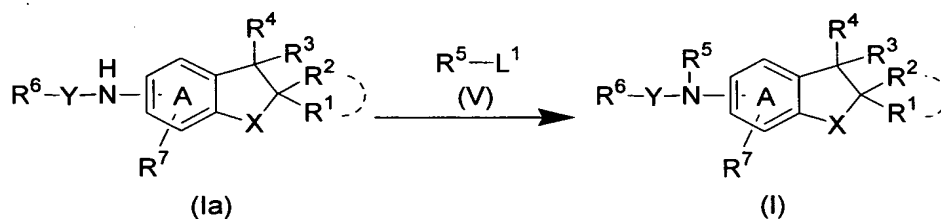
The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional
20 means of separation (e.g., recrystallization, distillation, chromatography, etc.).

[0021]

When R^5 is an optionally substituted alkyl group, Compound (I) can be produced according to a method
25 described in the following Reaction Scheme 2.

Reaction Scheme 2

[Chemical formula 26]



In Reaction Scheme 2, L^1 is a leaving group, and other
 5 symbols have the same meanings as defined above.

The "leaving group" represented by L^1 is, for example, hydroxy, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), optionally halogenated C_{1-5} alkylsulfonyloxy (e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, etc.), optionally substituted
 10 C_{6-10} arylsulfonyloxy, etc. Examples of the "optionally substituted C_{6-10} arylsulfonyloxy" include C_{6-10} arylsulfonyloxy (e.g., phenylsulfonyloxy, naphthylsulfonyloxy, etc.) which may have 1 to 3
 15 substituents selected from C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.) and nitro. Specific examples
 20 thereof include benzenesulfonyloxy, m-nitrobenzenesulfonyloxy, p-toluenesulfonyloxy, and the like.

Compound (Ia) is reacted with an alkylating agent (V)

corresponding to Compound (I), if desired, under the presence of base.

The alkylating agent (V) is used in an amount of about 1.0 to about 10.0 moles, preferably about 1.0 to about 2.0
5 moles, relative to 1 mole of Compound (Ia).

The "base" is, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, etc., aromatic amines such as pyridine, lutidine, etc., tertiary amines such as triethylamine,
10 tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc., alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide,
15 lithium diisopropylamide, lithium hexamethyldisilazide, etc., metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc., or the like.

The base is used in an amount of about 1.0 to about 10.0 moles, preferably about 1.0 to about 2.0 moles,
20 relative to 1 mole of Compound (Ia).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, alcohols such as methanol, ethanol,
25 propanol, etc., ethers such as diethyl ether,

tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as
 5 dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

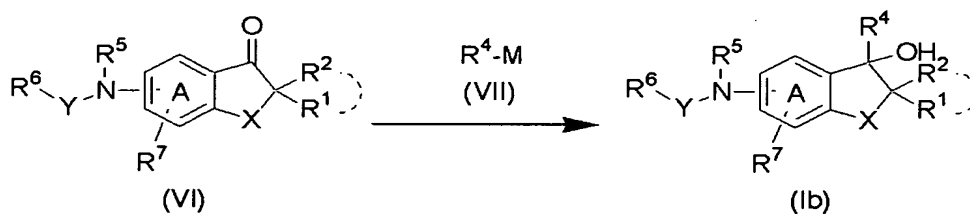
The reaction time is usually about 30 minutes to about
 10 48 hours, preferably about 1 hour to about 24 hours. The reaction temperature is usually about -20 to about 200°C, preferably about 0 to about 150°C.

[0022]

In addition, Compound (Ib) which is contained in
 15 Compound (I), can be also produced by a method described in the following Reaction Scheme 3.

Reaction Scheme 3

[Chemical formula 27]



20 In Reaction Scheme 3, M is a metal and other symbols have the same meanings as defined above.

In the formula, an organic metallic Compound (VII)

represented by R^4-M is commercially available, and further can be also produced by per se known methods, for example, the method described in Experimental Chemistry Lecture, 4th Ed., 25 (Japanese Society of Chemistry), Maruzen, Co., Ltd.

5 As shown in Reaction Scheme 3, Compound (Ib) is obtained by reacting Compound (VI) with the organic metallic Compound (VII).

The organic metallic Compound (VII) is preferably a Grignard reagent or an organic lithium reagent.

10 Compound (VII) is used in an amount of about 0.8 to about 30 moles, preferably about 1.0 to about 10 moles, relative to 1 mole of Compound (VI).

The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction.
15 Such solvents are not particularly limited if the reaction proceeds, and include, for example, hydrocarbons such as hexane, cyclohexane, benzene, toluene, xylene, etc., ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., halogenated carbons
20 such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., or a mixed solvent thereof, or the like.

The reaction time is usually about 10 minutes to about 24 hours, preferably about 30 minutes to about 5 hours.

25 The reaction temperature is usually about -100 to about

120°C, preferably about -80 to about 60°C.

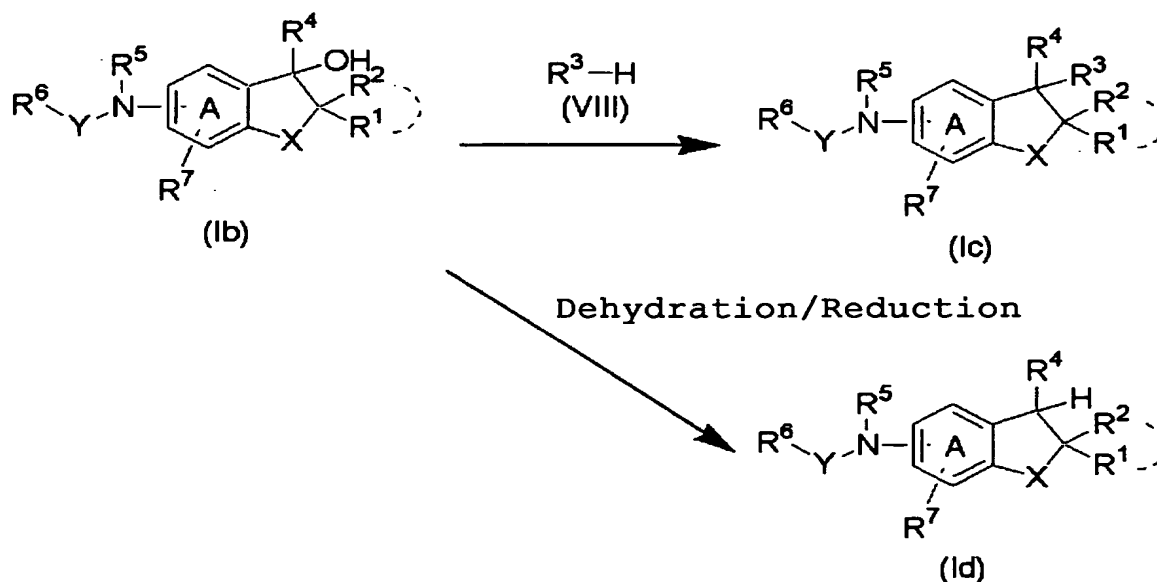
The product can be used in the next reaction as a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

[0023]

Compound (Ic) and Compound (Id), which are contained in Compound (I), can be produced by each method described in the following Reaction Scheme 4, respectively, from Compound (Ib) produced by the method described in Reaction Scheme 3, etc.

Reaction Scheme 4

[Chemical formula 28]



In Reaction Scheme 4, each symbol has the same meaning

as defined above.

Compound (Ib) is subjected to known acylation, etherification, amination, halogenation, alkylation, or a combination of two or more of these reactions, to produce
5 Compound (Ic).

For example, when R^3 is alkoxy (e.g., methoxy, ethoxy, phenoxy, etc.), Compound (Ib) is reacted with alcohol (e.g., methanol, ethanol, phenol, etc.) under the presence of acid catalyst to give Compound (Ic).

10 The "acid catalyst" is, for example, organic acids such as formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, etc., mineral acids such as sulfuric acid, hydrochloric acid, hydrobromic acid, etc., Lewis acids such as zinc chloride, etc.

15 The alcohol is used in an amount of about 0.8 moles to excessive amount, relative to 1 mole of Compound (Ib). The acid catalyst is used respectively in an amount of about 0.1 to about 100 moles, preferably about 0.1 to about 50 moles, relative to 1 mole of Compound (Ib).

20 The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, hydrocarbons such as hexane, cyclohexane, benzene, toluene, xylene, etc., ethers
25 such as diethyl ether, diisopropyl ether, tetrahydrofuran,

dioxane, 1,2-dimethoxyethane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc., sulfoxides such as dimethylsulfoxide, etc., halogenated carbons such as
5 dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., or a mixed solvent thereof, or the like.

The reaction time is usually about 10 minutes to about
10 48 hours, preferably about 30 minutes to about 12 hours. The reaction temperature is usually about 0 to about 200°C, preferably about 25 to about 100°C.

The product can be used in the next reaction as the reaction solution itself or the crude product, or can be
15 isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

In addition, Compound (Id) can be produced by
20 subjecting Compound (Ib) to reductive dehydration.

The reductive dehydration is, for example, per se known catalytic reduction, a method in which an organosilyl reagent (an alkylsilane reagent, etc.) is used, etc.

In the catalytic reduction, Compound (Ib) is reacted
25 with a metal catalyst under hydrogen atmosphere to produce

Compound (Id). A suitable acid catalyst may be added, if desired.

The "metal catalyst" is, for example, Raney nickel, platinum oxide, metal palladium, palladium on activated carbon, etc. The "metal catalyst" is used respectively in an amount of usually about 0.1 to about 1000% by weight, preferably about 1 to about 20% by weight, relative to Compound (Ib).

The "acid catalyst" is, for example, organic acids such as formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, etc., mineral acids such as sulfuric acid, hydrochloric acid, hydrobromic acid, etc. The "acid catalyst" is used respectively in an amount of about 0.1 to excessive amount, relative to 1 mole of Compound (Ib).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., organic acids such as acetic acid, etc., water, etc., or a mixed solvent thereof, or the like. The hydrogen pressure is usually about 1 to about 100 atm.,

preferably about 1 to about 5 atm. The reaction time is usually about 30 minutes to about 48 hours, preferably about 1 to 24 hours. The reaction temperature is usually about 0 to about 120°C, preferably about 20 to about 80°C.

5 After the catalyst is removed, the product may be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

10 In the method wherein the organosilyl reagent (alkylsilane reagent) is used, Compound (Id) can be produced by reacting Compound (Ib) with the alkylsilane reagent and an acid.

15 The alkylsilane reagent is, for example, triethylsilane, phenyldimethylsilane, etc. The "alkylsilane reagent" is used respectively in an amount of about 0.8 to about 20 moles, preferably about 1 to about 5 moles, relative to 1 mole of Compound (Ib).

20 The acid is, for example, organic acids such as trifluoroacetic acid, etc. The acid is used respectively in an amount of about 0.1 to excessive amount, relative to 1 mole of Compound (Ib).

25 The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction. Such solvents are not particularly limited if the reaction

proceeds, and include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., halogenated carbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., organic acids such as acetic acid, trifluoroacetic acid, etc., or a mixed solvent thereof, or the like.

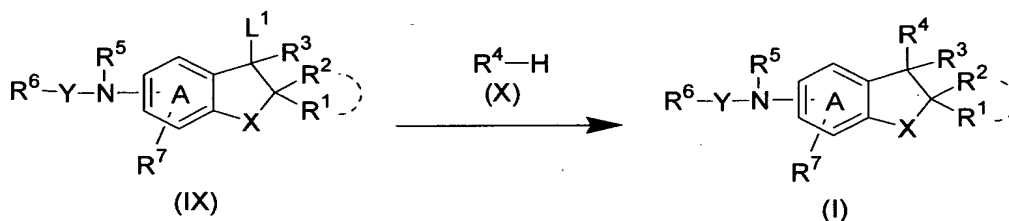
The product may be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

[0024]

When Compound (X) represented by R^4-H is amine, alcohol, thiol, phenol or thiophenol, Compound (I) corresponding to Compound (X) can be also produced by a method described in the following Reaction Scheme 5.

Reaction Scheme 5

[Chemical formula 29]



In Reaction Scheme 5, each symbol has the same meaning as defined above.

Compound (X) represented by R^4-H is commercially

available, and further can also be produced by per se known methods.

According to Reaction Scheme 5, Compound (I) is obtained by reacting Compound (IX) and Compound (X) under the presence of acid catalyst or base.

Compound (X) is used in an amount of about 1 mole to about 50 moles, preferably about 1 to about 5 moles, relative to 1 mole of Compound (IX).

The "acid catalyst" is, for example, organic acids such as formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, etc., mineral acids such as sulfuric acid, hydrochloric acid, hydrobromic acid, etc., Lewis acids such as zinc chloride, etc.

The "base" is, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, etc., aromatic amines such as pyridine, lutidine, etc., tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc., alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc., metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc., or the like.

The acid catalyst is used in an amount of about 0.1 moles to excessive amount, preferably about 0.1 to about 50 moles, relative to 1 mole of Compound (IX).

5 The base is used in an amount of about 1.0 to 5.0 moles, preferably about 1.0 to 2.0 moles, relative to 1 mole of Compound (IX).

The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction. Such solvents are not particularly limited if the reaction
10 proceeds, and include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-
15 dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

20 The reaction time is usually about 10 minutes to about 48 hours, preferably about 30 minutes to about 24 hours. The reaction temperature is usually -20 to 200°C, preferably 0 to 150°C.

Mitsunobu reaction (Synthesis, 1981, pp. 1 ~ 27) can
25 be also used in stead of the above-mentioned reaction.

This reaction is carried out by reacting Compound (X) and Compound (IX) wherein L^1 is OH, under the presence of azodicarboxylates (e.g., diethyl azodicarboxylate, etc.) and phosphines (e.g., triphenylphosphine, tributylphosphine, etc.).

Compound (X) is used in an amount of about 1.0 to 5.0 moles, preferably about 1.0 to 2.0 moles, relative to 1 mole of Compound (IX).

The "azodicarboxylates" and the "phosphines" are used in an amount of about 1.0 to 5.0 moles, preferably about 1.0 to 2.0 moles, respectively, relative to 1 mole of Compound (IX).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

The reaction time is usually 5 minutes to 48 hours,

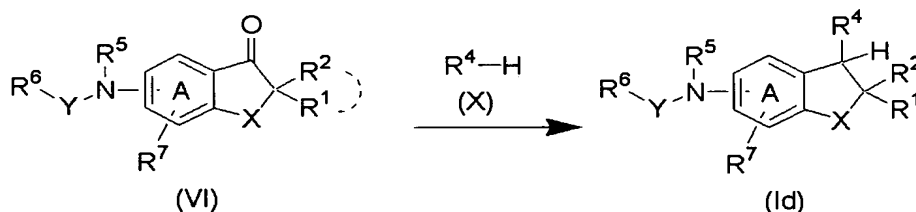
preferably 30 minutes to 24 hours. The reaction temperature is usually -20 to 200°C, preferably 0 to 100°C. The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

[0025]

When R^4 is an optionally substituted amino group, Compound (Id) which is contained in Compound (I), can also be produced by reductive amination described in the following Reaction Scheme 6.

Reaction Scheme 6

[Chemical formula 30]



In Reaction Scheme 6, R^4 is an optionally substituted amino group, and other symbols have the same meanings as defined above.

Compound (Id) is produced by condensing Compound (VI) and Compound (X) which is amine and reducing it with a reducing agent.

Compound (X) is used in an amount of about 1.0 to about 5.0 moles, preferably about 1.0 to about 2.0 moles, relative to 1 mole of Compound (VI).

The "reducing agent" is, for example, metal hydrides such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, etc., boranes such as borane tetrahydrofuran complex, etc., hydrosilanes such as triethylsilane, or formic acid, etc. Further acid catalyst may be added with the reducing agent, if desired. The acid catalyst is, for example, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc., sulfonic acids such as methanesulfonic acid, p-toluenesulfonic acid, etc., organic acids such as acetic acid, propionic acid, trifluoroacetic acid, etc., Lewis acids such as zinc chloride, aluminum chloride, etc.

The "reducing agent" is used in an amount of about 0.25 to about 5.0 moles, preferably about 0.5 to about 2.0 moles respectively, relative to 1 mole of Compound (VI).

The amount of the acid catalyst to be used is, for example, usually about 1 to about 100 moles, preferably about 1 to about 20 moles, relative to 1 mole of Compound (VI) when mineral acids are used.

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and

include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., or a mixed solvent thereof, or the like.

The reaction time is usually about 5 minutes to about 48 hours, preferably about 30 minutes to about 24 hours. The reaction temperature is usually about -20 to about 200°C, preferably about 0 to about 100°C.

This reaction is also carried out by condensation of Compound (VI) and Compound (X), followed by catalytic hydrogenation under hydrogen atmosphere under the coexistence of various catalysts, instead of reduction by reducing agent. The catalyst to be used is, for example, platinum oxide, platinum on activated carbon, palladium on activated carbon, nickel, copper-chrome oxide, rhodium, cobalt, ruthenium, etc. The catalyst is used in an amount of about 0.1 to about 1000% by weight, preferably about 1 to about 1000% by weight, relative to Compound (VI).

The present reaction is advantageously carried out

using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, water, etc., or a mixed solvent thereof, or the like.

The reaction time is usually about 30 minutes to about 48 hours, preferably about 30 minutes to about 24 hours. The reaction temperature is usually about 0 to about 120°C, preferably about 20 to about 80°C.

The product may be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

[0026]

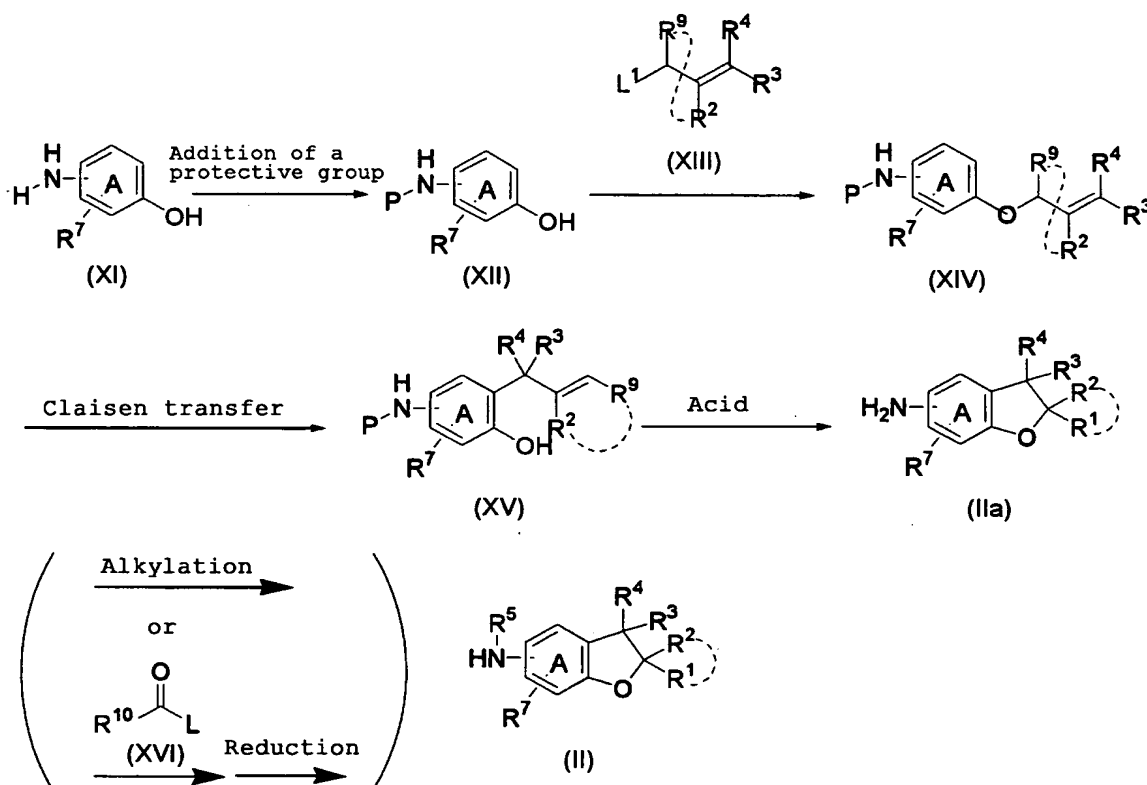
The above-mentioned Compound (II) is produced by, per se known methods, for example, the method described in JP-A H05-140142, or analogous methods thereto, etc.

In addition, Compound (IIa), a dihydrobenzofuran derivative which is contained in Compound (II), can be produced by per se known methods, for example, the method described in Reaction Scheme 7 or Reaction Scheme 8 below

which is described in WO 2003-004485, etc. Further, other compounds which are contained in Compound (II), can be also produced by known method from Compound (IIa), if necessary.

[0027]

5 Reaction Scheme 7
[Chemical formula 31]



In Reaction Scheme 7, R^9 is a hydrogen atom or a group formed by deducting one methylene from R^1 . R^{10} is a group formed by deducting one methylene from R^5 . Other symbols have the same meanings as defined above.

Obtained Compound (IIa) can be subjected to alkylation, if necessary. The alkylation can be carried out by

reacting Compound (IIa) with an alkylating agent corresponding to the objective compound (II), if desired, under the presence of base.

5 The alkylating agent is used in an amount of about 1.0 to about 5.0 moles, preferably about 1.0 to about 2.0 moles, relative to 1 mole of Compound (IIa).

10 The "base" is, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, etc., aromatic amines such as pyridine, lutidine, etc., tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc., alkali metal hydrides such as sodium hydride, 15 potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc., metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc., or the like.

20 The base is used in an amount of about 1.0 to about 5.0 moles, preferably about 1.0 to about 2.0 moles, relative to 1 mole of Compound (IIa).

25 The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, alcohols such as methanol, ethanol,

propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

10 The reaction time is usually about 30 minutes to about 48 hours, preferably about 1 hour to about 24 hours. The reaction temperature is usually about -20 to about 200°C, preferably about 0 to about 150°C.

15 Alternatively, a method can be used wherein Compound (IIa) and Compound (XVI) are reacted, if desired, under the presence of base or acid to produce acylamide, which is reduced by a reducing agent.

20 Compound (XVI) is used in an amount of about 1.0 to 5.0 moles, preferably about 1.0 to 2.0 moles, relative to 1 mole of Compound (IIa).

 The "base" is, for example, organic bases such as triethylamine, pyridine, etc.

 The "acid" is, for example, methanesulfonic acid, p-toluenesulfonic acid, camphor-sulfonic acid, etc.

25 The "base" is used in an amount of about 0.1 to 10

equivalents, preferably 0.8 to 2 equivalents, relative to Compound (IIa).

The "acid" is used in an amount of about 0.1 to 10 equivalents, preferably 0.8 to 3 equivalents, relative to
5 Compound (IIa).

The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, ethers such as diethyl
10 ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-
15 dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., nitrogen-containing aromatic hydrocarbons such as pyridine, lutidine, quinoline, etc., or a mixed solvent thereof, or the like. The reaction temperature is about -
20 20 to 150°C, preferably 0 to 100°C. The reaction time is usually 5 minutes to 24 hours, preferably 10 minutes to 5 hours.

Thus obtained acylamide can be used in the next reaction as a reaction solution as is or a crude product,
25 or can be isolated from the reaction mixture according to a

conventional method, and easily purified by conventional means of separation such as recrystallization, distillation, chromatography, etc.

5 The reducing agent is, for example, metal hydrides such as sodium borohydride, lithium aluminum hydride, etc., boranes such as borane tetrahydrofuran complex, etc.

In addition, an acid catalyst may be added with the reducing agent, if desired. The acid catalyst is, for example, Lewis acids such as trifluoroborane diethyl ether
10 complex, aluminum chloride, etc.

The reducing agent is used respectively in an amount of about 0.25 to about 10 moles, preferably about 0.5 to about 5 moles, relative to 1 mole of acylamide.

The Lewis acids are used respectively in an amount of
15 about 0.25 to about 10 moles, preferably about 0.5 to about 5 moles, relative to 1 mole of acylamide.

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and
20 include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, water, etc., or a mixed solvent thereof, or the like.

25 The reaction time is usually about 30 minutes to about

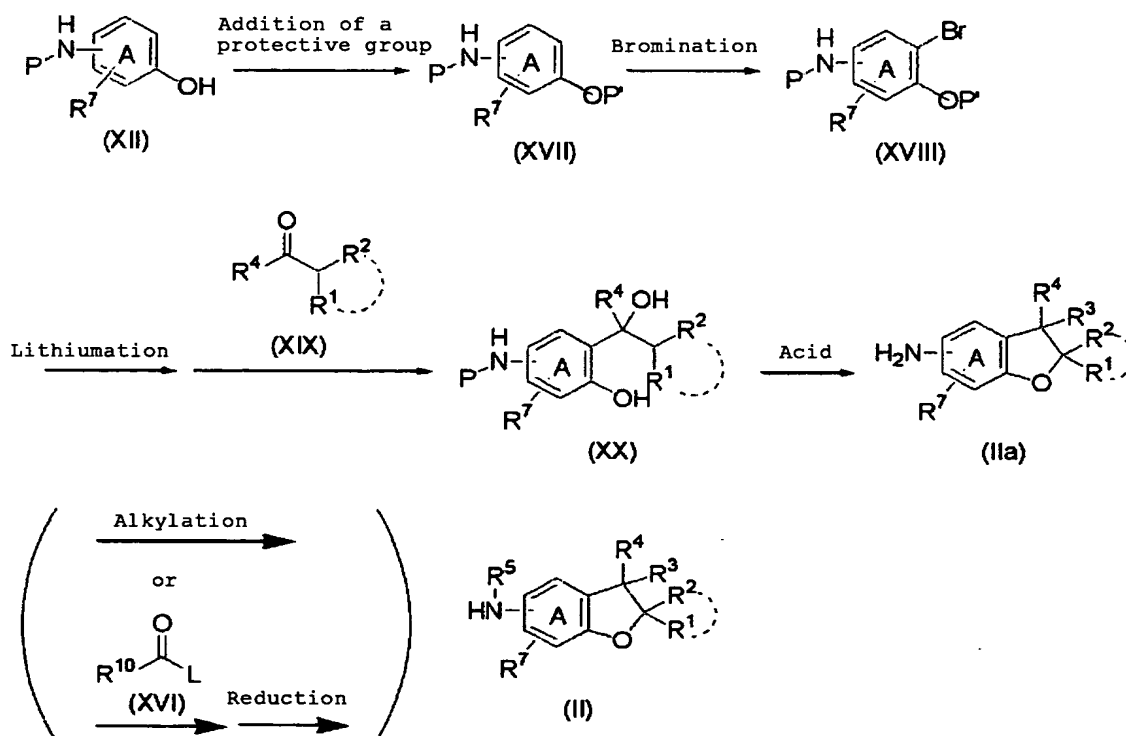
24 hours, preferably about 1 hour to about 16 hours. The reaction temperature is usually about 0 to about 150°C, preferably about 20 to about 100°C.

Thus obtained product (II) can be used in the method described in Reaction Scheme (I) as a reaction solution as is or a crude product, can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation such as recrystallization, distillation, chromatography, etc.

[0028]

Reaction Scheme 8

[Chemical formula 32]



In Reaction Scheme 8, P' is a protective group of

hydroxyl group, and other symbols have the same meanings as defined above.

Compound (XVII) is produced by subjecting Compound (XII) to addition of a protective group which is generally
5 used in the peptide chemistry, etc.

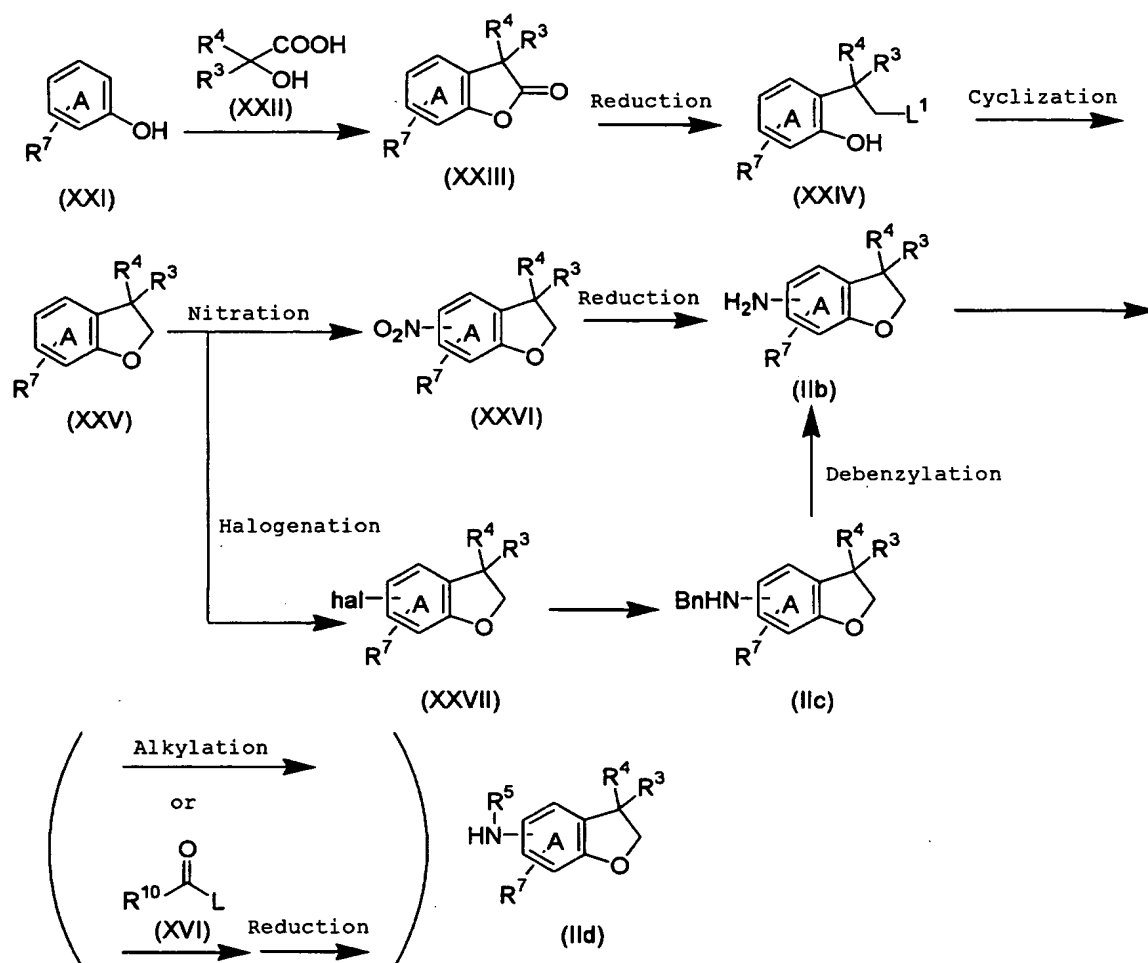
Compound (IIa) is provided to the next reaction, if necessary, as in the method described in Reaction Scheme 7.

[0029]

In addition, Compounds (IIb), (IIc), and (IId) which
10 are contained in Compound (II), are also produced by a method described in the following Reaction Scheme 9.

Reaction Scheme 9

[Chemical formula 33]



In Reaction Scheme 9, hal is a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), and other symbols have the same meanings as defined above.

5 Compound (XXIII) can be produced by reacting Compound (XXI) with Compound (XXII) under acidic condition.

Compound (XXI) is commercially available, and further can be also produced by per se known methods, for example, the method described in Experimental Chemistry Lecture 20,
 10 4th Ed., (Japanese Society of Chemistry), 111 to 185,

Maruzen, Co., Ltd. and analogous methods thereto.

Compound (XXII) is commercially available, and further can be also produced by per se known methods and analogous methods thereto.

5 The "acid" is, for example, Lewis acids such as aluminum chloride, iron chloride, stannous chloride, titanium tetrachloride, boron trifluoride diethyl ether, etc., mineral acids such as polyphosphoric acid, sulfuric acid, etc., organic acids such as trifluoroacetic acid,
10 methanesulfonic acid, p-toluenesulfonic acid, trifluoromethanesulfonic acid, etc.

 The acid is used in an amount of, for example, usually about 0.5 to about 100 moles, preferably about 10 to about 50 moles, relative to 1 mole of Compound (XXI) when mineral
15 acids are used, and usually about 0.1 to about 20 moles, preferably about 0.1 to about 5 moles, relative to 1 mole of Compound (XXI) when sulfonic acids are used.

 The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction.
20 Such solvents are not particularly limited if the reaction proceeds. For example, when mineral acids are used, the solvent is, preferably a mixed solvent of water and organic solvents such as saturated hydrocarbons such as cyclohexane, hexane, etc., aromatic hydrocarbons such as benzene,
25 toluene, xylene, etc., ethers such as tetrahydrofuran,

dioxane, 1,2-dimethoxyethane, diethyl ether, diisopropyl ether, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., or water.

5 The reaction time is usually about 30 minutes to about 24 hours, preferably about 30 minutes to about 6 hours. The reaction temperature is usually about -78 to about 200°C, preferably about -20 to about 150°C.

10 The product can be used in the next reaction as a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

15 Compound (XXIV) is produced by reducing Compound (XXIII).

20 The reducing agent is, for example, metal hydrides such as aluminum hydride, diisobutylaluminum hydride, etc., complex metal hydrides such as sodium borohydride, lithium borohydride, lithium aluminum hydride, sodium aluminum bis(2-methoxyethoxy) hydride, etc., borane complexes such as borane tetrahydrofuran complex, borane dimethylsulfide, etc., alkylboranes such as hexylborane, disiamylborane, etc., diborane, etc.

25 In addition, an acid catalyst may be added with the reducing agent, if desired. The acid catalyst is, for

example, Lewis acids such as trifluoroborane diethyl ether complex, aluminum chloride, etc.

The reducing agent is used respectively in an amount of about 0.25 to about 10 moles, preferably about 0.5 to about 5 moles, relative to 1 mole of Compound (XXIII).

The Lewis acids are used respectively in an amount of about 0.25 to about 10 moles, preferably about 0.5 to about 5 moles, relative to 1 mole of Compound (XXIII).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, water, etc., or a mixed solvent thereof, or the like.

The reaction time is usually about 30 minutes to about 24 hours, preferably about 1 hour to about 16 hours. The reaction temperature is usually about 0 to about 150°C, preferably about 20 to about 100°C.

Thus obtained product (XXIV) can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation, such as recrystallization, distillation, chromatography, etc.

Compound (XXV) is produced by converting Compound (XXIV) (e.g., the compound in which L¹ is hydroxy) to sulfonate or halide, and subjecting it to cyclization. The sulfonate compound is synthesized by reacting Compound (XXIV) and corresponding sulfonyl chloride compound (for example, benzenesulfonyl chloride, toluenesulfonyl chloride, C₁₋₄ alkylsulfonyl chloride such as methanesulfonyl chloride, etc.) under the presence of base.

The sulfonyl chloride compound is used respectively in an amount of about 1.0 to about 10 moles, preferably about 1.0 to about 5 moles, relative to 1 mole of Compound (XXIV).

The base is, for example, organic bases such as triethylamine, pyridine, etc.

The base is used respectively in an amount of about 1.0 to about 50 moles, preferably about 1.0 to about 20 moles, relative to 1 mole of Compound (XXIV).

The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as

dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., nitrogen-containing aromatic hydrocarbons such as
5 pyridine, lutidine, quinoline, etc., or a mixed solvent thereof, or the like. The reaction temperature is about -78 to 150°C, preferably -30 to 100°C. The reaction time is usually 5 minutes to 24 hours, preferably 10 minutes to 5 hours.

10 The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation,
15 chromatography, etc.).

[0031]

The halide is synthesized by reacting Compound (XXIV) and a halogenating agent (for example, phosphorus halide such as phosphorus trichloride, phosphorus oxychloride,
20 phosphorus pentachloride, phosphorus tribromide, etc., halogen, thionyl chloride, etc.).

The halogenating agent is used in an amount of about 1.0 to about 100 moles, preferably about 1.0 to about 10 moles, relative to 1 mole of Compound (XXIV). The present
25 reaction is advantageously carried out without a solvent or

with a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like. The reaction temperature is about 0 to 200°C, preferably 10 to 100°C. The reaction time is usually 10 minutes to 24 hours, preferably 10 minutes to 5 hours.

The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

[0032]

Compound (XXV) is also synthesized by subjecting thus obtained sulfonate compound or halide to cyclization under the presence of base. The base is, for example, organic bases such as triethylamine, pyridine, etc.

The base is used respectively in an amount of about 1.0 to about 50 moles, preferably about 1.0 to about 20 moles, relative to 1 mole of the sulfonate compound or halide.

5 The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl
10 ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-
15 dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., esters such as ethyl acetate, etc., water or mixed solvent thereof, or the like. The reaction temperature is about -10 to 250°C, preferably 0 to 120°C. The reaction time is usually 10 minutes to 6 hours,
20 preferably 10 minutes to 2 hours.

The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional
25 means of separation (e.g., recrystallization, distillation,

chromatography, etc.).

[0033]

Alternatively, Mitsunobu reaction (Synthesis, 1981, pp. 1-27) can be also used.

5 In this reaction, Compound (XXIV) in which L^2 is OH, is subjected to intra-molecular cyclization under the presence of azodicarboxylates (e.g., diethyl azodicarboxylate, etc.) and phosphines (e.g., triphenylphosphine, tributylphosphine, etc.) to give
10 Compound (XXV).

The "azodicarboxylates" and the "phosphines" are used respectively in an amount of about 1.0 to 5.0 moles, preferably about 1.0 to 2.0 moles, relative to 1 mole of Compound (XXIV).

15 The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.,
20 hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile,
25 propionitrile, etc., sulfoxides such as dimethylsulfoxide,

etc., or a mixed solvent thereof, or the like.

The reaction time is usually 5 minutes to 48 hours, preferably 30 minutes to 24 hours. The reaction temperature is usually -20 to 200°C, preferably 0 to 100°C.

5 [0034]

In addition, Compound (XXVI) can be synthesized by nitrating Compound (XXV). The nitrating agent is, for example, mixed acid, acetyl nitrate, fuming nitric acid, potassium nitrate, ammonium nitrate, nitronium
10 tetrafluoroborate, nitronium trifluoromethanesulfonate, etc. The nitrating agent is used in an amount of about 1.0 to about 50 moles, preferably about 1.0 to about 10 moles, relative to 1 mole of Compound (XXV). The present reaction is advantageously carried out without a solvent or with a
15 solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, organic acids such as acetic acid, trifluoroacetic acid, etc., acid anhydride such as acetic anhydride, trifluoroacetic anhydride, etc., mineral acids
20 such as sulfuric acid, nitric acid, etc., saturated hydrocarbons such as hexane, cyclohexane, etc., halogenated carbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., or a mixed solvent thereof, or the like.

25 The reaction time is usually about 10 minutes to about

24 hours, preferably about 10 minutes to about 16 hours. The reaction temperature is usually about -10 to about 200°C, preferably about -10 to about 120°C.

The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

[0035]

Compound (IIb) is produced by reducing Compound (XXVI), and then alkylating, if desired.

The reducing agent which is used in the reduction is, for example, metal hydrides such as aluminum hydride, diisobutylaluminum hydride, etc., complex metal hydrides such as sodium borohydride, lithium aluminum hydride, etc., borane complexes such as borane tetrahydrofuran complex, borane dimethylsulfide, etc., alkylboranes such as hexylborane, disiamylborane, etc., diborane, or metals such as zinc, aluminum, tin, iron, etc., alkali metals (sodium, lithium, etc.)/liquid ammonia (Birch Reduction), etc. Further, the hydrogenating catalyst is, for example, palladium carbon, platinum oxide, Raney nickel, Raney cobalt, etc. The hydrogen source is, for example, formic acid, ammonium formate, hydrazine, etc. in addition to gas-

phase hydrogen.

The "reducing agent" is used in an amount of, for example, about 1.0 to about 10 moles, preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (XXVI) when metal hydrides or complex metal hydride is used, about 1.0 to about 10 moles, preferably about 1.0 to about 5.0 moles when borane complexes, alkylboranes or diborane is used, and about 1.0 to about 20 equivalents, preferably about 1.0 to about 5.0 equivalents when metals or alkali metals are used to 1 mole of Compound (XXVI). In case of hydrogenation, the catalyst such as palladium carbon, platinum oxide, Raney nickel, Raney cobalt, etc. is used in an amount of about 5 to 1000% by weight, preferably about 10 to 300% by weight, relative to Compound (XXVI). When the hydrogen source other than gas-phase hydrogen is used, it is used in an amount of about 1.0 to about 20 moles, preferably about 2.0 to about 10 moles, relative to 1 mole of Compound (XXVI).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane,

etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., organic acids such as formic acid, acetic acid, water, etc., or a mixed solvent thereof, or the like. When the catalyst of Raney nickel or Raney cobalt is used, amines such as ammonia, etc. may be further added to inhibit reverse reaction.

The reaction time is varied depending on kinds or amount of reducing agent, or activity or amount of catalyst, but usually about 1 hour to about 100 hours, preferably about 1 hour to about 50 hours. The reaction temperature is usually about 0 to about 150°C, preferably about 20 to about 100°C. When a hydrogenation catalyst is used, hydrogen pressure is usually 1 to 100 atm.

Thus obtained product (IIb) can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation such as recrystallization, distillation, chromatography, etc.

Compound (XXVII) is produced by reacting Compound (XXV) and a halogenating reagent.

The "halogenating reagent" is, for example, chlorine, bromine, iodine, imides such as N-chlorosuccinimide or N-bromosuccinimide, etc., halogen adducts such as benzyltrimethylammonium tribromide, etc. The "halogenating reagent" is used in an amount of about 0.8 to about 5.0 moles, preferably about 1.0 to about 2.0 moles, relative to

1 mole of Compound (XXV).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and
5 include, for example, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., alcohols such as methanol, ethanol, propanol, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-
10 dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., organic acids such as acetic acid,
15 propionic acid, etc., nitroalkanes such as nitromethane, etc., aromatic amines such as pyridine, lutidine, quinoline, etc., or a mixed solvent thereof, or the like.

The present reaction is carried out under the presence of base or Lewis acid or iron, if desired.

20 The "base" is, for example, basic salts such as sodium carbonate, calcium carbonate, cesium carbonate, sodium hydrogen carbonate, sodium acetate, potassium acetate, etc., aromatic amines such as pyridine, lutidine, etc., tertiary amines such as triethylamine, tripropylamine, tributylamine,
25 cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-

dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. The base is used in an amount of about 0.8 to about 10 moles, relative to 1 mole of Compound (XXV).

5 The "Lewis acid" is, for example, iron chloride, aluminum chloride, boron trifluoride, etc. The Lewis acid is used in an amount of about 0.01 to about 5 moles, relative to 1 mole of Compound (XXV).

10 The "iron" is used in an amount of about 0.01 to about 5 moles, relative to 1 mole of Compound (XXV).

The reaction temperature is usually about -50 to about 150°C, preferably about -20 to about 100°C. The reaction time is usually about 5 minutes to about 24 hours, preferably about 10 minutes to about 12 hours.

15 In addition, when a halogen atom is substituted on ring A of Compound (XXI), Compound (XXVII) can be produced without halogenation.

20 The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

25 Compound (IIc) is produced by reacting Compound (XXVII) and benzylamine, if desired, under the presence of

base. If necessary, a catalyst such as copper, copper salt, etc. may be used, or a catalyst such as palladium or nickel, etc. and a ligand (for example, phosphine or pyridines, etc.) may be also used according to the method described in
5 Chemistry Letters, 1983, pp. 927-928.

The benzylamine is used in an amount of about 0.8 to about 10.0 moles, preferably about 1.0 to about 5.0 moles, relative to 1 mole of Compound (XXVII).

The "base" is, for example, basic salts such as sodium
10 carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, etc., aromatic amines such as pyridine, lutidine, etc., tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine,
15 etc., alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc., metal alkoxides such as sodium methoxide, sodium
20 ethoxide, sodium tert-butoxide, potassium tert-butoxide, etc., or the like.

The "base" is used in an amount of about 0.8 to about 10.0 moles, preferably about 1.0 to about 5.0 moles, relative to 1 mole of Compound (XXVII).

25 The present reaction is advantageously carried out

using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

The "copper catalyst" is, for example, copper, halogenated copper (CuI, CuBr, CuCl, etc.), copper oxide (CuO), etc. The copper catalyst is used in an amount of about 0.1 to about 10.0 moles, preferably about 0.5 to about 2.0 moles, relative to 1 mole of Compound (XXVII).

The "ligand" is preferably phosphines such as trialkylphosphine, triarylphosphine, trialkoxyphosphine, etc. The palladium catalyst is, for example, palladium acetate, palladium chloride, tetrakis(triphenylphosphine)palladium, bis(dibenzylideneacetone)palladium, etc.

The "phosphine" is used in an amount of about 0.001 to about 10.0 moles, preferably about 0.01 to about 1.0 mole,

relative to 1 mole of Compound (XXVII). The palladium catalyst is used in an amount of about 0.001 to about 5.0 moles, preferably about 0.01 to about 0.5 moles, relative to 1 mole of Compound (XXVII).

5 The reaction time is usually about 30 minutes to about 72 hours, preferably about 1 hour to about 48 hours. The reaction temperature is usually about -20 to about 200°C, preferably about 0 to about 150°C.

10 The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

15 Compound (IIb) is produced by debenzylation of Compound (IIc).

20 The debenzylation is carried out by per se known reaction, for example, the method described in T.W. Green, Protective Groups in Organic Synthesis, 3rd Ed., 1999, Chapter of "Protection for the Amino Group", etc.

25 The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation,

chromatography, etc.).

Compound (IIId) is produced from Compound (IIb) by the same method in which Compound (IIb) is produced from Compound (IIa), if necessary.

5 [0036]

In addition, when Compound (IIe) which is contained in Compound (II) is a benzofuran derivative, the compound can be produced by per se known methods, for example, the method described in Reaction Scheme 10 below as the method
10 described in WO 2003-004485. Compound (II) can be produced from Compound (IIe), if necessary.

Reaction Scheme 10

[Chemical formula 34]

15 In Reaction Scheme 10, each symbol has the same meaning as defined above.

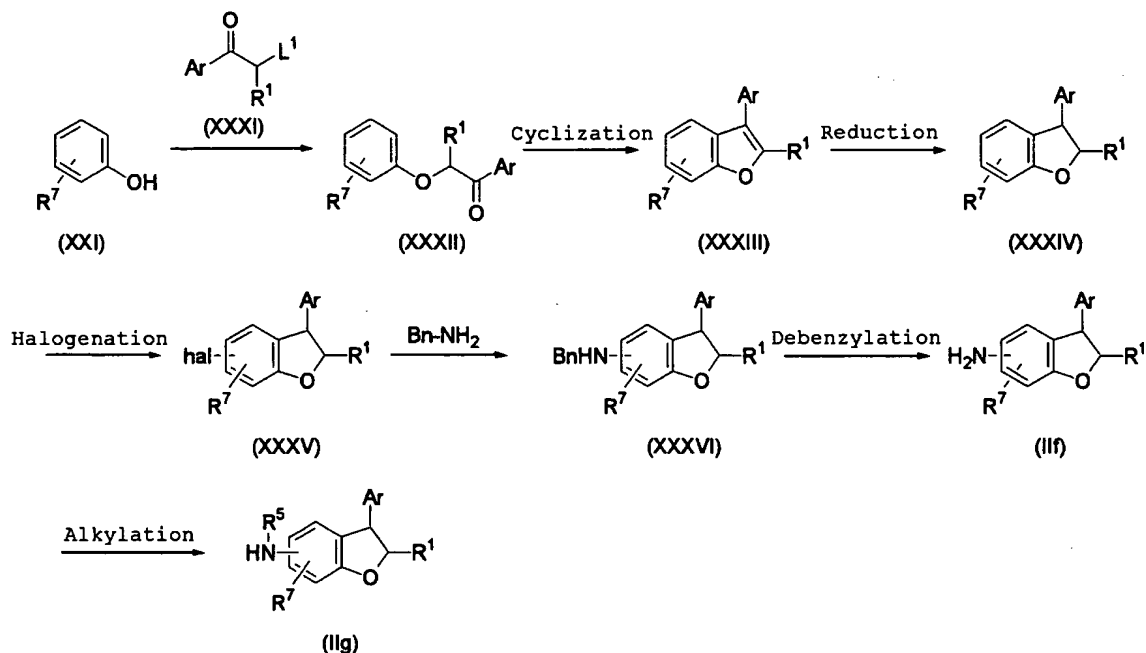
Compound (II) is produced from Compound (IIe) by a similar method to that for producing Compound (IIb) from Compound (IIa), if desired.

20 [0037]

When R^3 is an aromatic ring, Compound (IIIf) and Compound (IIg) which are contained in Compound (II), are also produced by a method described in the following Reaction Scheme 11.

25 Reaction Scheme 11

[Chemical formula 35]



In Reaction Scheme 11, Ar is an optionally substituted aromatic ring (e.g., benzene ring, naphthalene ring, pyridine ring, furan ring, thiophene ring, etc.), L^2 is a leaving group, and each symbol has the same meaning as defined above.

Compound (XXXI) is commercially available, and further can be also produced by per se known methods.

Compound (XXXII) is produced by reacting Compound (XXI) and Compound (XXXI), if desired, under the presence of base.

The "base" is, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, etc., aromatic amines such as pyridine,

lutidine, etc., tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc., alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc., metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc., or the like.

10 Compound (XXXI) is used in an amount of about 0.7 to about 5.0 moles, preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (XXI).

15 The base is used in an amount of about 0.8 to about 5.0 moles, preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (XXI). Further, if desired, quaternary ammonium salt may be combined and reacted with the base in producing Compound (XXXII).

 The "quaternary ammonium salt" is, for example, tetrabutylammonium iodide, etc.

20 The quaternary ammonium salt is used in an amount of about 0.1 to about 2.0 moles, preferably about 0.5 to about 1.0 mole, relative to 1 mole of Compound (XXI).

25 The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and

include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

10 The reaction time is usually about 30 minutes to about 96 hours, preferably about 1 hour to about 72 hours. The reaction temperature is usually about 0 to about 120°C, preferably about 0 to about 60°C.

15 Mitsunobu reaction (Synthesis, 1981, pp. 1-27) can be also used in stead of the above-mentioned reaction.

20 This reaction is carried out by reacting Compound (XXI) and Compound (XXXI) in which L^2 is OH under the presence of azodicarboxylates (e.g., diethyl azodicarboxylate, etc.) and phosphines (e.g., triphenylphosphine, tributylphosphine, etc.).

Compound (XXXI) is used in an amount of about 0.8 to about 5.0 moles, preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (XXI).

25 The "azodicarboxylates" and the "phosphines" are used respectively in an amount of about 0.8 to about 5.0 moles,

preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (XXI).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

The reaction time is usually about 5 minutes to about 48 hours, preferably about 30 minutes to about 24 hours. The reaction temperature is usually about -20 to about 200°C, preferably about 0 to about 100°C.

The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

Compound (XXXIII) is produced by subjecting Compound

(XXXII) to per se known cyclization.

For this cyclization, an acid is used.

The "acid" is, for example, Lewis acids such as aluminum chloride, iron chloride, stannous chloride, titanium tetrachloride, boron trifluoride diethyl ether, etc., mineral acids such as polyphosphoric acid, sulfuric acid, etc., organic acids such as trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, trifluoromethanesulfonic acid, etc., acidic resin or clay such as zeolite, Amberlite, Montmorillonite, etc., or the like.

The "acid" is used respectively in an amount of catalytic amount to excessive amount relative to Compound (XXXII), preferably about 0.8 to about 5 moles, relative to 1 mole of Compound (XXXII). The acidic resin or clay is used in an amount of about 0.1 to 50 grams, preferably 1 to 5 grams, relative to 1 gram of Compound (XXXII).

The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., carbon disulfide, nitroalkanes such as nitromethane, etc., nitroaryls such as nitrobenzene, etc., halogenated

carbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, 1,2-dichlorobenzene, etc., organic acids such as acetic acid, trifluoroacetic acid, etc., or a mixed solvent thereof, or the like.

5 The reaction time is usually about 10 minutes to about 96 hours, preferably about 30 minutes to about 16 hours. The reaction temperature is usually about -70 to about 200°C, preferably about -20 to about 150°C.

10 The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

15 Compound (XXXIII) is produced by reducing Compound (XXXII).

20 The reduction is carried out by per se known reaction, for example, using catalyst such as palladium carbon, etc. under hydrogen atmosphere. After the catalyst is removed, the product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

25

Compound (XXXV) is produced by reacting Compound (XXXIV) and halogenating reagent.

The "halogenating reagent" is, for example, chlorine, bromine, iodine, imides such as N-chlorosuccinimide or N-bromosuccinimide, etc., halogen adducts such as benzyltrimethylammonium tribromide, etc., or the like. The halogenating reagent is used in an amount of about 0.8 to about 5.0 moles, preferably about 1.0 to about 2.0 moles, relative to 1 mole of Compound (XXXIV).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., alcohols such as methanol, ethanol, propanol, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., organic acids such as acetic acid, propionic acid, etc., nitroalkanes such as nitromethane, etc., aromatic amines such as pyridine, lutidine, quinoline, etc., or a mixed solvent thereof, or the like.

The present reaction is carried out under the presence of base or Lewis acid or iron, if desired.

The "base" is, for example, basic salts such as sodium carbonate, calcium carbonate, cesium carbonate, sodium hydrogen carbonate, sodium acetate, potassium acetate, etc., aromatic amines such as pyridine, lutidine, etc., tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. The base is used in an amount of about 0.8 to about 10 moles, relative to 1 mole of Compound (XXXIV).

The "Lewis acid" is, for example, iron chloride, aluminum chloride, boron trifluoride, etc. The Lewis acid is used in an amount of about 0.01 to about 5 moles, relative to 1 mole of Compound (XXXIV).

The "iron" is used in an amount of about 0.01 to about 5 moles, relative to 1 mole of Compound (XXXIV).

The reaction temperature is usually about -50 to about 150°C, preferably about -20 to about 100°C. The reaction time is usually about 5 minutes to about 24 hours, preferably about 10 minutes to about 12 hours. The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily

purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

In addition, when a halogen atom is substituted on a benzene ring of Compound (XXI), Compound (XXXV) can be
5 produced without halogenation.

Compound (XXXVI) is produced by reacting Compound (XXXV) and benzylamine, if desired, under the presence of base. If necessary, a catalyst such as copper, copper salt, etc. may be used, or a catalyst such as palladium or nickel,
10 etc. and a ligand (for example, phosphine or pyridines, etc.) may be also used according to the method described in Chemistry Letters, 1983, pp. 927-928 catalyst.

The benzylamine is used in an amount of about 0.8 to about 10.0 moles, preferably about 1.0 to about 5.0 moles,
15 relative to 1 mole of Compound (XXXV).

The "base" is, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, etc., aromatic amines such as pyridine, lutidine, etc., tertiary amines such as triethylamine,
20 tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc., alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide,
25 lithium diisopropylamide, lithium hexamethyldisilazide,

etc., metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, etc., or the like.

The base is used in an amount of about 0.8 to about 5 10.0 moles, preferably about 1.0 to about 5.0 moles, relative to 1 mole of Compound (XXXV).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and 10 include, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N- 15 dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

20 The copper catalyst is, for example, copper, halogenated copper (CuI, CuBr, CuCl, etc.), copper oxide (CuO), etc.

The copper catalyst is used in an amount of about 0.1 to about 10.0 moles, preferably about 0.5 to about 2.0 25 moles, relative to 1 mole of Compound (XXXV).

The "ligand" is preferably phosphines such as trialkylphosphine, triarylphosphine, trialkoxyphosphine, etc. The palladium catalyst is, for example, palladium acetate, palladium chloride, tetrakis(triphenylphosphine)palladium, bis(dibenzylideneacetone)palladium, etc.

The phosphine is used in an amount of about 0.001 to about 10.0 moles, preferably about 0.01 to about 1.0 mole, relative to 1 mole of Compound (XXXV). Palladium catalyst is used in an amount of about 0.001 to about 5.0 moles, preferably about 0.01 to about 0.5 moles, relative to 1 mole of Compound (XXXV).

The reaction time is usually about 30 minutes to about 72 hours, preferably about 1 hour to about 48 hours. The reaction temperature is usually about -20 to about 200°C, preferably about 0 to about 150°C. The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

Compound (IIIf) is produced by debenzylation of Compound (XXXVI).

The debenzylation is carried out by per se known reaction, for example, the method described in T.W. Green,

Protective Groups in Organic Synthesis, 3rd Ed., 1999, Chapter of "Protection for the Amino Group", etc. The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

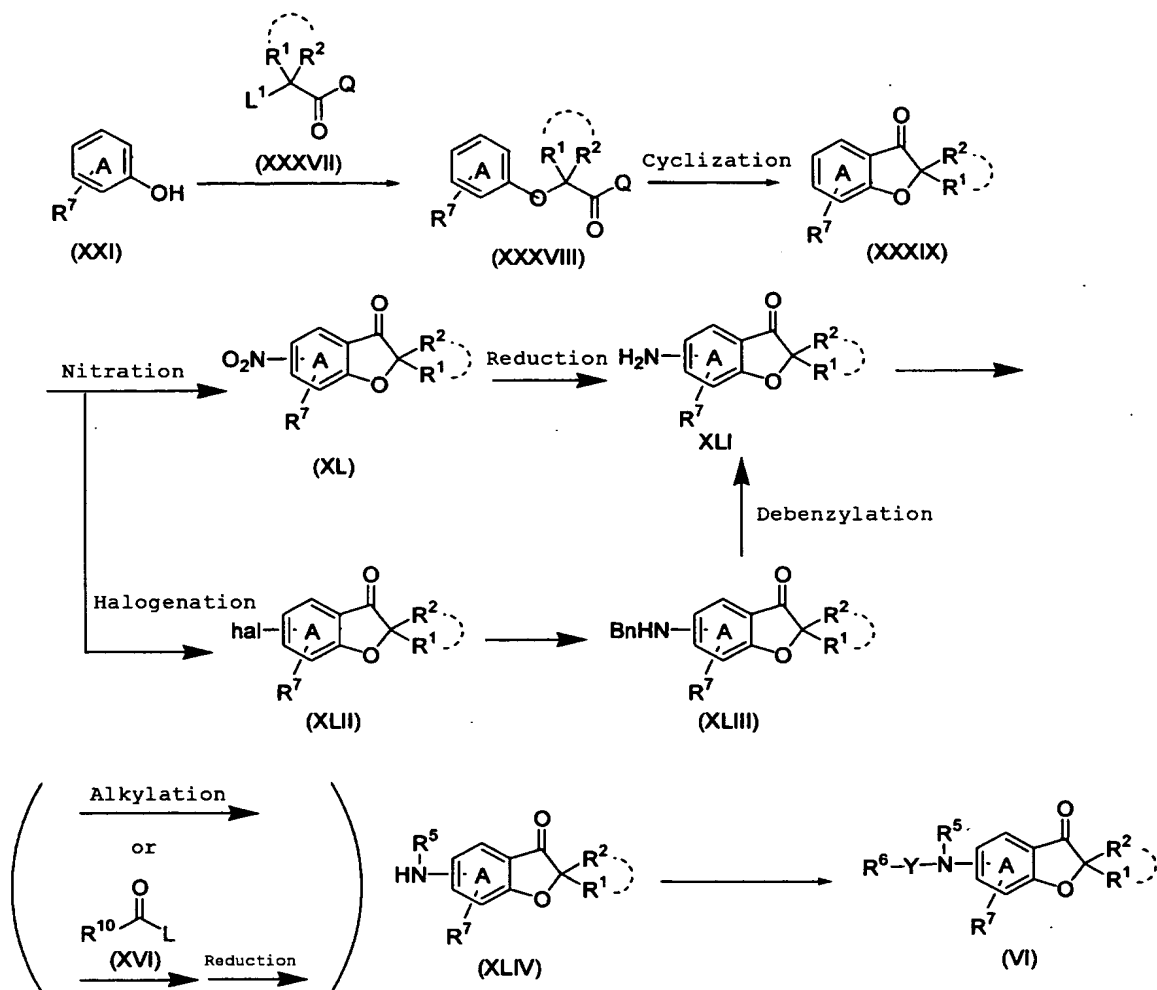
Compound (IIg) is produced from Compound (IIf) by the same method as that for producing Compound (IIb) from Compound (IIa), if necessary.

[0038]

In addition, when Compound (VI) is a benzofuran, the compound is also produced by a method described in the following Reaction Scheme 12.

Reaction Scheme 12

[Chemical formula 36]



In Reaction Scheme 12, the group represented by $-CO-Q$ is carboxylic acid or a reactive derivative thereof, and other symbols have the same meanings as defined above.

5 Compound (XXXVIII) is produced by reacting Compound (XXI) and Compound (XXXVII), if desired, under the presence of base.

The "base" is, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, etc., aromatic amines such as pyridine,

10

lutidine, etc., tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc., alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc., metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc., or the like.

10 Compound (XXXVII) is used in an amount of about 0.8 to about 5.0 moles, preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (XXI).

15 The base is used in an amount of about 0.8 to about 5.0 moles, preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (XXI). Further, if desired, quaternary ammonium salt may be added with the base in producing Compound (XXXVIII).

 The "quaternary ammonium salt" is, for example, tetrabutylammonium iodide, etc.

20 The quaternary ammonium salt is used in an amount of about 0.1 to about 2.0 moles, preferably about 0.5 to about 1.0 mole, relative to 1 mole of Compound (XXI).

25 The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and

include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

The reaction time is usually about 30 minutes to about 96 hours, preferably about 1 hour to about 72 hours. The reaction temperature is usually about 0 to about 120°C, preferably about 0 to about 60°C.

Mitsunobu reaction (Synthesis, 1981, pp. 1-27) can be also used in stead of the above-mentioned reaction.

This reaction is carried out by reacting Compound (XXI) and Compound (XXXVII) in which L^2 is OH under the presence of azodicarboxylates (e.g., diethyl azodicarboxylate, etc.) and phosphines (e.g., triphenylphosphine, tributylphosphine, etc.).

Compound (XXXVII) is used in an amount of about 0.8 to about 5.0 moles, preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (XXI).

The "azodicarboxylates" and the "phosphines" are used respectively in an amount of about 0.8 to about 5.0 moles,

preferably about 1.0 to about 3.0 moles, relative to 1 mole of Compound (XXI).

The present reaction is advantageously carried out using a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons such as dichloromethane, chloroform, tetrachlorocarbon, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., sulfoxides such as dimethylsulfoxide, etc., or a mixed solvent thereof, or the like.

The reaction time is usually about 5 minutes to about 48 hours, preferably about 30 minutes to about 24 hours. The reaction temperature is usually about -20 to about 200°C, preferably about 0 to about 100°C.

The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

Compound (XXXIX) is produced by subjecting Compound

(XXXVIII) to per se known cyclization.

Q in the formula is preferably, a hydroxyl group, a halogen atom, etc. In this reaction, Compound (XXXVIII) is reacted with acid to give Compound (XXXIX), if desired.

5 The "acid" is, for example, Lewis acids such as aluminum chloride, iron chloride, stannous chloride, titanium tetrachloride, boron trifluoride diethyl ether, etc., mineral acids such as polyphosphoric acid, sulfuric acid, etc., organic acids such as trifluoroacetic acid,
10 methanesulfonic acid, p-toluenesulfonic acid, trifluoromethane sulfonic acid, etc.

 The "acid" is used respectively in an amount of catalytic amount to excessive amount relative to Compound (XXXVIII), preferably about 0.8 to about 5 moles, relative
15 to 1 mole of Compound (XXXVIII).

 The present reaction is advantageously carried out without a solvent or with a solvent inert to the reaction. Such solvents are not particularly limited if the reaction proceeds, and include, for example, carbon disulfide,
20 nitroalkanes such as nitromethane, etc., nitroaryls such as nitrobenzene, etc., halogenated carbons such as dichloromethane, 1,2-dichloroethane, 1,2-dichlorobenzene, etc., organic acids such as acetic acid, trifluoroacetic acid, etc., acid anhydride such as acetic anhydride,
25 trifluoroacetic anhydride, etc., or a mixed solvent thereof,

or the like.

The reaction time is usually about 10 minutes to about 96 hours, preferably about 10 minutes to about 12 hours. The reaction temperature is usually about -70 to about 200°C, preferably about -40 to about 150°C.

The product can be used in the next reaction as a reaction solution as is or a crude product, or can be isolated from the reaction mixture according to a conventional method, and easily purified by conventional means of separation (e.g., recrystallization, distillation, chromatography, etc.).

Compound (XLIV) is produced from Compound (XXXIX) by the same method as the method of producing Compound (IIId) from Compound (XXV).

Compound (VI) is produced from Compound (XLIV) by the same method as the method of producing Compound (I) from Compound (II).

[0039]

The compounds which are raw materials for the above-mentioned Compound (I), etc. may form a salt. Kinds of the salt are not particularly limited if the reactions are achieved, and include, for example, the salts that the above-mentioned Compound (I), etc. may form.

Configurational isomers ((E)- and (Z)-forms) of Compound (I), etc. and Compounds (Ia), (Ib), (Ic) and (Id)

which are contained in Compound (I), and Compound (I'), can be isolated and purified by conventional means of separation such as extraction, recrystallization, distillation, chromatography, etc. to produce pure compounds at the point when the isomers are generated. Further, the corresponding pure isomers can be also obtained by progressing isomerization of a double bond with an acid catalyst, a transitional metal complex, a metal catalyst, a radical species catalyst, an illumination or a strong base catalyst, or by heating, etc., according to the method described in New Experimental Chemistry Lecture 14 (Japanese Society of Chemistry), pp. 251-253, Experimental Chemistry Lecture 19 (Japanese Society of Chemistry), 4th Ed., pp. 273-274 and analogous methods thereto.

In addition, stereoisomers of Compound (I), etc. are generated depending on kinds of substituents, and these isomers which are isolated or mixed, are contained in the present invention.

Compound (I), etc. may be a hydrate or a non-hydrate.

In any case, Compound (I), etc. can be synthesized by deprotection, acylation, alkylation, hydrogenation, oxidation, reduction, carbon chain extension reaction, substituent exchange reaction, or a combination of two or more, if further desired.

When the objective compound is obtained in free form,

it can be converted to a salt by a conventional method. When the objective compound is obtained in salt form, it can be converted to free form or another salt by a conventional method. Thus obtained Compound (I), etc. can
5 be isolated and purified from the reaction solution by known means such as solvent conversion, concentration, solvent extraction, fractional distillation, crystallization, recrystallization, chromatography, etc.

When compound (I) exists as configurational isomers,
10 diastereomers, conformers, etc., the respective isomers can be isolated by the above-mentioned means of isolation and purification. Further, when compound (I), etc. are racemic compounds, they can be separated into (d) and (l) forms by any conventional optical resolution means.

15 In the above reactions, when the starting compounds have a functional group such as an amino group, a hydroxyl group, a carboxyl group, etc., these groups may be protected by conventional protective groups such as those generally employed in peptide chemistry, and the like,
20 followed by subjecting to a reaction. After the reaction, the protective groups may be removed to obtain the objective compound, if necessary.

The protective group is, for example, formyl or, C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl, etc.),
25 phenylcarbonyl, C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl,

ethoxycarbonyl, etc.), phenyloxycarbonyl, C₇₋₁₀ aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, etc.), trityl, phthaloyl, etc, each of which may be substituted. The substituent thereof is, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl, valeryl, etc.), nitro, etc. The number of the substituent is, for example, 1 to 3.

In addition, the protective group may be removed by per se known methods or analogous methods thereto, for example, a method of treating the protective group with an acid, a base, ultraviolet ray, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, etc., or reduction.

[0040]

Compound (I₀) and a prodrug thereof have a cannabinoid receptor (particularly CB1) agonistic action, and useful for treating and preventing various diseases as described in Clin. Pharmacokinet., 2003 42(4) 327-360. Specific examples include, but are not limited to, cerebrovascular disorders such as cerebral infarction, cerebral hemorrhage, etc.; head injury; spinal damage; atmospheric hypoxia and ischemia by nerve gas damage; nausea, vomit by anticancer agent; low appetite such as anorexia, cachexia, etc. in cancer and AIDS; nausea by emetics; seizure by multiple sclerosis; psychogenic pain; chronic pain; Tourette's

syndrome, imbalance; motor function disorders such as levodopa-induced motor disorders, etc.; asthma; glaucoma; allergy; inflammation; epilepsy; refractory hiccup; depression; bipolar depression; anxiety; dependency and withdrawal syndrome on opiate and alcohol; renal diseases such as renal failure, etc.; various syndromes of Alzheimer's dementia; autoimmune diseases such as multiple sclerosis, arthritis, rheumatism, Crohn's Disease, etc.; hypertension; cancer; diarrhea; respiratory tract obstruction; sleep apnea, etc.

Compound (I) and a prodrug thereof are preferred based on this perspective. Further, a compound wherein the 2-position of the fused heterocyclic ring represented by formula (I₀) and (I) is not substituted (that is, both of R¹ and R² are a hydrogen atom, for example, Compound (I')) is particularly preferred.

[0041]

Compound (I₀), Compound (I) and a prodrug thereof have a cannabinoid receptor (in particular, CB1) antagonistic action, and useful for, but are not limited to, treating and preventing anxiety, mood disorders, delirium, general mental diseases, schizophrenia, depression, drug use-related diseases such as alcohol dependency, nicotine dependency, etc., neuropathy, migraine, mental stress, epilepsy, motor disorders such as dyskinesia of Parkinson's

disease, memory disorders, cognitive disorders, panic disorders, Parkinson's disease, Huntington chorea, Raynaud's Disease, tremor, obsessive-compulsive syndrome, geriatric or Alzheimer's disease, hyperkinesia, wake
5 disorders, neuro-protection in neurodegenerative diseases, appetite suppression in intake disorders, excessive appetite, overeating and obesity, type II diabetes mellitus, digestive tract disorders, diarrhea, ulcer, vomit, urinary tract or bladder function disorders, circulation disorders,
10 infertility, inflammatory pneumonia, infection, anticancer, smoking cessation, endotoxin shock, bleeding shock, hypotension and insomnia, and further, pain-relieving, potentiating opiate or non-opiate analgesics, and improving digestive tract movement. As pharmacological tools in
15 human or animal, the compounds can be used as itself or with a form labeled with radioisotope for detecting and labeling CB1 receptor.

Compound (I) and a prodrug thereof are preferred based on this perspective. Further, a compound wherein the 2-
20 position of the fused heterocyclic ring represented by formula (I₀) and (I) is substituted (that is, both of R¹ and R² are a substituent other than hydrogen atom (particularly preferably C₁₋₄ alkyl)) is particularly preferred.

The compound of the present invention has low toxicity and can safely be administered orally or parenterally (e.g. topically, rectally, intravenously, etc.) alone or in the form of a pharmaceutical composition prepared by
5 formulating it with a pharmacologically acceptable carrier according to per se known means in such dosage forms as tablets (including sugar-coated and film-coated tablets, intraoral disintegrating tablets), powders, granules, capsules (including soft capsules), solutions, injections,
10 suppositories, controlled release dosage forms and adhesive preparations.

[0043]

The content of the compound of the present invention in the preparation of the present invention is about 0.001
15 to about 100% by weight based on the total weight of the preparation.

The dosage is varied depending on the subject to be administered, the route of administration, the disease to be treated, and other factors. For example, when an
20 injectable dosage form is administered to an adult patient for the treatment of a head injury, the dosage of the compound of the present invention in terms of active ingredient is about 0.001 to about 20 mg/kg body weight, preferably about 0.005 to about 5 mg/kg body weight, and
25 more preferably about 0.05 to about 1 mg/kg body weight per

day in a single dose or in divided doses.

The present compound can be used in combination with other active ingredients [(e.g., a thrombolytic agent (e.g., tissue plasminogen activator, urokinase, etc.), an anticoagulant (e.g., argatroban, warfarin, etc.), Factor X-inhibitor, thromboxane-synthetase inhibitor, (e.g., ozagrel, etc.), an antioxidant (e.g., edaravon, etc.), an anti-edema agent (e.g., glycerol, mannitol, etc.), neuropoiesis or nerve regeneration promoter (e.g., Akt/PKB activator, GSK-3 β -inhibitor, etc.), acetylcholinesterase inhibitor (e.g., donepezil, rivastigmine, galantamine, zanapezil, etc.), a suppressor for production, secretion, accumulation, aggregation and/or deposition of β -amyloid protein [β -secretase inhibitor (e.g. the compound described in WO 98/38156, the compound described in WO 02/2505, WO 02/2506 or WO 02/2512, OM99-2 (WO 01/00663)), γ -secretase inhibitor, inhibitor of β -amyloid protein aggregation (e.g., PTI-00703, ALZHEMED (NC-531), PPI-368 (JP-A H11-514333), PPI-558 (JP-A 2001-500852), SKF-74652 (Biochem. J.(1999),340(1),283-289)), β -amyloid vaccine, β -amyloid decomposing enzyme, etc.], brain function enhancing agent (e.g., aniracetam, nicergoline, etc.), other treating agent for Parkinson's disease [(e.g., dopamine receptor agonist (L-dopa, bromocriptine, pergolide, talipexol, pramipexol, cabergoline, adamantadine, etc.), monoamine oxidase (MAO)

inhibitor (Deprenyl, selegiline, remacemide, riluzole, etc.), anticholinergics (e.g., trihexyphenidyl, biperiden, etc.), COMT inhibitor (e.g., entacapone, etc.)], an agent of treating amyotrophic lateral sclerosis (e.g., riluzole, etc., neuro-nutrition factor, etc.), an agent of treating hyperlipidemia such as a cholesterol-lowering agent, etc. [statins (e.g., fluvastatin sodium, atorvastatin, simvastatin, rosuvastatin, etc.), fibrate (e.g., clofibrate, etc.), squalene-synthetase inhibitor], an agent of treating abnormal behavior, loitering, etc. which are involved in dementia (e.g., sedatives, anxiolytics, etc.), apoptosis inhibitor (e.g., CPI-1189, IDN-6556, CEP-1347, etc.), an agent of promoting differentiating and regenerating nerves (Leteprinim, Xaliproden (SR-57746-A), SB-216763, etc.), anti-hypertensives, an agent of treating diabetes mellitus, anti-depressive, anxiolytics, non-steroid anti-inflammatory agent (e.g., meloxicam, tenoxicam, indometacin, ibuprofen, celecoxib, rofecoxib, aspirin, etc.), disease-modifying anti-rheumatic drugs (DMARDs), anti-cytokine drugs (TNF inhibitor, MAP kinase inhibitor, etc.), steroids (e.g., dexamethasone, hexesterol, cortisone acetate, etc.), sexual hormones or derivatives thereof (e.g., progesterone, estradiol, estradiol benzoate, etc.), para-thyroid hormone (PTH), calcium receptor antagonist, etc.]. These other active ingredients can be formulated in combination with

the compound of the present invention or a salt thereof according to per se known methods to provide a pharmaceutical composition (e.g., tablets, powders, granules, capsules (including soft capsules), solutions, injections, suppositories, controlled release dosage forms, etc.), or can be formulated separately to be administered to the same subject at the same time or at time interval.

[0044]

The pharmacologically acceptable carrier that can be used in the manufacture of a pharmaceutical composition of the present invention includes various kinds of organic or inorganic carriers which are conventionally used in pharmaceutical practice, such as excipient, lubricant, binder, and disintegrator for solid preparations; or the solvent, solubilizer, suspending agent, isotonicizing agent, buffer, and soothing agent for liquid preparations. Further, common additives such as antiseptics, antioxidant, colorant, sweetener, adsorbent, wetting agent, etc. can also be incorporated, if necessary.

The excipient includes, for example, lactose, sucrose, D-mannitol, starch, corn starch, crystalline cellulose, light silicic anhydride, etc.

The lubricant includes, for example, magnesium stearate, calcium stearate, talc, colloidal silica, etc.

The binder includes, for example, crystalline

cellulose, sucrose, D-mannitol, dextrin,
hydroxypropylcellulose, hydroxypropylmethylcellulose,
polyvinylpyrrolidone, starch, cane sugar, gelatin,
methylcellulose, carboxymethylcellulose sodium, etc.

5 The disintegrator includes, for example, starch,
carboxymethylcellulose, carboxymethylcellulose calcium,
croscarmellose sodium, carboxymethyl starch sodium, L-
hydroxypropylcellulose, etc.

The solvent includes, for example, water for injection,
10 alcohol, propylene glycol, macrogols, sesame oil, corn oil,
olive oil, etc.

The solubilizer includes, for example, polyethylene
glycol, propylene glycol, D-mannitol, benzyl benzoate,
ethanol, trisaminomethane, hydrophilic surfactant such as
15 Tween 80 (trademark), cholesterol, cyclodextrin (for
example, α -, β - or γ -cyclodextrin or 2-hydroxypropyl- β -
cyclodextrin or methyl- β -cyclodextrin, etc.)
triethanolamine, sodium carbonate, sodium citrate, etc.

The suspending agent includes, for example,
20 surfactants such as stearyltriethanolamine, sodium lauryl
sulfate, laurylaminopropionic acid, lecithin, benzalkonium
chloride, benzethonium chloride, glyceryl monostearate,
etc.; and hydrophilic polymers such as polyvinyl alcohol,
polyvinylpyrrolidone, carboxymethylcellulose sodium,
25 methylcellulose, hydroxymethylcellulose,

hydroxyethylcellulose, hydroxypropylcellulose, etc.

The isotonizing agent includes, for example, glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol, etc.

5 The buffer includes, for example, buffer solutions such as phosphate, acetate, carbonate, citrate, etc.

The soothing agent includes, for example, benzyl alcohol, etc.

10 The antiseptic includes, for example, paraoxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

The antioxidant includes, for example, sulfites, ascorbic acid, α -tocopherol, etc.

[0045]

15 The following Reference Examples, Examples, Formulation Examples and Experimental examples are intended to describe the present invention in further detail and should by no means be construed as defining the scope of the invention, and further can be changed without departing from the scope of the present invention.

20 As used in the following reference and working examples, the term "room temperature" generally means about 10 to 35°C. The symbol % stands for percentage by weight unless otherwise indicated.

25 The other abbreviations used in the text have the following meanings.

s: singlet

d: doublet

dd: doublet of doublets

dt: doublet of triplets

5 t: triplet

q: quartet

septet: septet

m: multiplet

br: broad

10 J: coupling constant

Hz: Hertz

CDCl_3 : deuterated chloroform

DMSO-d_6 : deuterated dimethylsulfoxide

$^1\text{H-NMR}$: proton nuclear magnetic resonance

15 THF: tetrahydrofuran

DMF: dimethylformamide

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

For $^1\text{H-NMR}$, proton on a hydroxyl group or an amino group has very gentle peak, is not indicated. Further,
20 data for a free form was described as a free base for a compound forming a salt.

Kieselgel 60 made by Merk was used for silica gel chromatography, and Chromatorex NH made by Fuji Silica Chemistry, Co., Ltd was used for basic silica gel
25 chromatography.

[0046]

Reference Example 1

Hydroxy(4-isopropylphenyl)acetic acid

To a mixture of lithium chloride (17.0 g, 418 mmol),
5 potassium hydroxide (44.9 g, 800 mmol) and ice (150 g) was
added a solution of bromoform (17.5 mL, 200 mmol) and 4-
isopropyl benzaldehyde (30.3 mL, 200 mmol) in 1,4-dioxane
(150 mL) at 0°C, and the mixture was stirred at 5-10°C for
24 hours and then stirred at 35°C for 24 hours. The
10 reaction mixture was diluted with water, and extracted with
diethyl ether. The aqueous layer was acidified with
hydrochloric acid and was extracted with ethyl acetate.
The extract was washed with water and then was dried over
anhydrous sodium sulfate. The solvent was distilled off
15 under reduced pressure to obtain a residue, which was
crystallized from hexane - ethyl acetate to obtain 28.5 g
(yield 73%) of the title compound. Melting point: 156 -
157°C.

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, J = 7.0 Hz), 2.91 (1H,
20 septet, J = 7.0 Hz), 5.21 (1H, s), 7.24 (2H, d, J = 8.8 Hz),
7.36 (2H, d, J = 8.8 Hz), 2H unidentified.

[0047]

Reference Example 2

3-(4-Isopropylphenyl)-4,6,7-trimethyl-1-benzofuran-2(3H)-
25 one

To a mixture of hydroxy(4-isopropylphenyl)acetic acid synthesized in Reference Example 1 (11.8 g, 60.8 mmol) and 2,3,5-trimethylphenol (12.4 g, 91.2 mmol) was added 70% sulfuric acid (10 mL) at room temperature, and the mixture was stirred at 115°C for 12 hours. The mixture was added to water and was extracted with diisopropyl ether. The extract was washed with water and a saturated sodium hydrogen carbonate solution, and then was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain a residue, which was purified by silica gel column chromatography (hexane : ethyl acetate = 8 : 1) to obtain 10.9 g (yield 65%) of the title compound. Melting point: 107 - 108°C (hexane - ethyl acetate).

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, J = 6.6 Hz), 1.93 (3H, s), 2.24 (3H, s), 2.29 (3H, s), 2.88 (1H, septet, J = 6.6 Hz), 4.76 (1H, s), 6.76 (1H, s), 7.07 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 8.1 Hz).

[0048]

Reference Example 3

3-(4-Isopropylphenyl)-6,7-dimethyl-1-benzofuran-2(3H)-one

Using hydroxy(4-isopropylphenyl)acetic acid synthesized in Reference Example 1 and 2,3-dimethylphenol, the title compound was synthesized in the same manner as in Reference Example 2. Yield 44%. Melting point: 58 - 60°C

(methanol).

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, J = 6.9 Hz), 2.27 (3H, s),
2.32 (3H, s), 2.88 (1H, septet, J = 6.6 Hz), 4.85 (1H, s),
6.91 (1H, d, J = 7.8 Hz), 6.95 (1H, d, J = 7.8 Hz), 7.13
5 (2H, d, J = 8.1 Hz), 7.19 (2H, d, J = 8.1 Hz).

[0049]

Reference Example 4

3-(4-Isopropylphenyl)-4,6-dimethyl-1-benzofuran-2(3H)-one

Using hydroxy(4-isopropylphenyl)acetic acid

10 synthesized in Reference Example 1 and 3,5-dimethylphenol,
the title compound was synthesized in the same manner as in
Reference Example 2. Yield 45%. Melting point: 76 - 77°C.
(ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, J = 7.0 Hz), 1.97 (3H, s),
15 2.38 (3H, s), 2.88 (1H, septet, J = 7.0 Hz), 4.73 (1H, s),
6.78 (1H, s), 6.84 (1H, s), 7.07 (2H, d, J = 8.2 Hz), 7.18
(2H, d, J = 8.2 Hz).

[0050]

Reference Example 5

20 5-Bromo-3-(4-isopropylphenyl)-1-benzofuran-2(3H)-one

Using hydroxy(4-isopropylphenyl)acetic acid

synthesized in Reference Example 1 and 4-bromophenol, the
title compound was synthesized in the same manner as in
Reference Example 2. Yield 30%. Melting point: 157 -
25 158°C. (methanol).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, d, $J = 6.9$ Hz), 2.90 (1H, septet, $J = 6.9$ Hz), 4.86 (1H, s), 7.06 (1H, d, $J = 8.7$ Hz), 7.11 (2H, d, $J = 8.4$ Hz), 7.23 (2H, d, $J = 8.4$ Hz), 7.33 (1H, s), 7.47 (1H, d, $J = 8.7$ Hz).

5 [0051]

Reference Example 6

3-(4-Isopropylphenyl)-3,4,6,7-tetramethyl-1-benzofuran-2(3H)-one

To a solution of 3-(4-isopropylphenyl)-4,6,7-trimethyl-1-benzofuran-2(3H)-one synthesized in Reference Example 2 (2.10 g, 7.13 mmol) in DMF (30 mL) was added sodium hydride (a 60% fluidized paraffin dispersion, 314 mg, 7.84 mmol) at 0°C , and the mixture was stirred at room temperature for 30 minutes. To the reaction solution was added methyl iodide (1.11 g, 7.84 mmol) and the mixture was stirred for at room temperature 30 minutes. Water was added to the reaction solution and the product was extracted with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure to obtain the residue, which was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 2.07 g (yield 94%) of the title compound as an oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (6H, d, $J = 6.9$ Hz), 1.94 (3H, s), 1.98 (3H, s), 2.25 (3H, s), 2.29 (3H, s), 2.87 (1H, septet,

25

$J = 6.9 \text{ Hz}$), 6.77 (1H, s), 7.09-7.22 (4H, m).

[0052]

Reference Example 7

3-(4-Isopropylphenyl)-3,6,7-trimethyl-1-benzofuran-2(3H)-
5 one

Using 3-(4-isopropylphenyl)-6,7-dimethyl-1-benzofuran-2(3H)-one synthesized in Reference Example 3, the title compound was synthesized in the same manner as in Reference Example 6. Yield 59%. Oily matter.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (6H, d, $J = 6.8 \text{ Hz}$), 1.87 (3H, s), 2.28 (3H, s), 2.33 (3H, s), 2.87 (1H, septet, $J = 6.9 \text{ Hz}$), 6.94 (1H, d, $J = 7.8 \text{ Hz}$), 6.94 (1H, d, $J = 7.8 \text{ Hz}$), 7.17 (2H, d, $J = 8.4 \text{ Hz}$), 7.25 (2H, d, $J = 8.4 \text{ Hz}$).

[0053]

15 Reference Example 8

2-(2-Hydroxy-1-(4-isopropylphenyl)ethyl)-3,5,6-trimethylphenol

To a solution of 3-(4-isopropylphenyl)-4,6,7-trimethyl-1-benzofuran-2(3H)-one (8.42 g, 28.6 mmol)
20 obtained in Reference Example 2 in THF (80 mL) was added lithium aluminum hydride (1.63 g, 42.9 mmol) at 0°C , and the mixture was heated under reflux for 1 hour. Water was added to the reaction solution and the product was
25 extracted with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate and then

concentrated under reduced pressure. The obtained residue was crystallized from hexane - ethyl acetate to obtain 8.00 g (yield 94%) of the title compound. Melting point: 101 - 102°C.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (6H, d, $J = 6.9$ Hz), 2.13-2.35 (10H, m), 2.86 (1H, septet, $J = 6.9$ Hz), 4.24 (1H, dd, $J = 10.8$ Hz), 4.42 (1H, dd, $J = 10.8, 5.1$ Hz), 4.50 (1H, dd, $J = 5.1, 2.7$ Hz), 6.58 (1H, s), 7.15 (4H, s), 8.01 (1H, br s).

[0054]

10 Reference Example 9

6-(2-Hydroxy-1-(4-isopropylphenyl)ethyl)-2,3-dimethylphenol

Using 3-(4-isopropylphenyl)-6,7-dimethyl-1-benzofuran-2(3H)-one synthesized in Reference Example 3, the title compound was synthesized in the same manner as in Reference
15 Example 8.

Yield 36%. Melting point: 83 - 84°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, d, $J = 7.2$ Hz), 2.03 (1H, br s), 2.18 (3H, s), 2.25 (3H, s), 2.87 (1H, septet, $J = 7.2$ Hz),
20 4.18-4.39 (3H, m), 6.68 (1H, d, $J = 7.8$ Hz), 6.77 (1H, d, $J = 7.8$ Hz), 6.84 (1H, s), 7.14 (2H, d, $J = 9.0$ Hz), 7.18 (2H, d, $J = 9.0$ Hz).

[0055]

Reference Example 10

25 2-(2-Hydroxy-1-(4-isopropylphenyl)ethyl)-3,5-dimethylphenol

Using 3-(4-isopropylphenyl)-4,6-dimethyl-1-benzofuran-2(3H)-one synthesized in Reference Example 4, the title compound was synthesized in the same manner as in Reference Example 8. Yield 93%. Melting point: 101 - 102°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, J = 6.9 Hz), 2.19 (3H, s), 2.25 (3H, s), 2.27 (1H, br s), 2.86 (1H, septet, J = 6.9 Hz), 4.21 (1H, dd, J = 11.1, 2.7 Hz), 4.39 (1H, dd, J = 11.1, 5.1 Hz), 4.48 (1H, dd, J = 5.1, 2.7 Hz), 6.57 (1H, s), 6.62 (1H, s), 7.15 (4H, s), 8.14 (1H, br s).

[0056]

Reference Example 11

4-Bromo-2-(2-hydroxy-1-(4-isopropylphenyl)ethyl)phenol

Using 5-bromo-3-(4-isopropylphenyl)-1-benzofuran-2(3H)-one synthesized in Reference Example 5, the title compound was synthesized in the same manner as in Reference Example 8. Yield 44%. Oily matter.

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, J = 6.9 Hz), 1.38 (1H, br s), 2.88 (1H, septet, J = 7.2 Hz), 4.18-4.37 (3H, m), 6.76 (1H, d, J = 8.1 Hz), 7.08-7.25 (6H, m), 7.47 (1H, br s).

[0057]

Reference Example 12

2-(2-Hydroxy-1-(4-isopropylphenyl)-1-methylethyl)-3,5,6-trimethylphenol

Using 3-(4-isopropylphenyl)-3,4,6,7-tetramethyl-1-

benzofuran-2(3H)-one synthesized in Reference Example 6, the title compound was synthesized in the same manner as in Reference Example 8. Yield 83%. Melting point: 116 - 117°C (ethyl acetate - hexane).

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (6H, d, $J = 6.9$ Hz), 1.73 (6H, s), 2.20 (3H, s), 2.21 (3H, s), 2.56-2.64 (1H, m), 2.88 (1H, septet, $J = 6.9$ Hz), 3.77 (1H, dd, $J = 11.1, 3.6$ Hz), 4.13-4.22 (1H, m), 6.49 (1H, s), 7.11 (2H, d, $J = 8.4$ Hz), 7.15 (2H, d, $J = 8.4$ Hz), 8.70 (1H, s).

10 [0058]

Reference Example 13

3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran

To a solution of 2-(2-hydroxy-1-(4-isopropylphenyl)ethyl)-3,5,6-trimethylphenol obtained in
15 Reference Example 8 (7.85 g, 26.3 mmol) and triphenylphosphine (7.58 g, 28.9 mmol) in THF (60 mL) was added diethyl azodicarboxylate (a 40% toluene solution, 12.6 g, 28.9 mmol) with ice-cooling, and the mixture was
20 stirred at room temperature for 1 hour. The solvent was concentrated under reduced pressure to obtain the residue, which was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to obtain 5.70g (yield 84%) of the title compound. Melting point: 48 - 49°C
25 (methanol).

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, J = 6.9 Hz), 1.89 (3H, s), 2.15 (3H, s), 2.23 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 4.37-4.56 (2H, m), 4.79-4.88 (1H, m), 6.48 (1H, s), 7.06 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz).

5 [0059]

Reference Example 14

3-(4-Isopropylphenyl)-6,7-dimethyl-2,3-dihydro-1-benzofuran

Using 6-(2-hydroxy-1-(4-isopropylphenyl)ethyl)-2,3-dimethylphenol synthesized in Reference Example 9, the
10 title compound was synthesized in the same manner as in
Reference Example 13. Yield 80%. Melting point: 50 - 51°C
(methanol).

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, J = 6.9 Hz), 2.18 (3H, s), 2.25 (3H, s), 2.88 (1H, septet, J = 6.9 Hz), 4.35-4.42 (1H,
15 m), 4.62 (1H, t, J = 8.7 Hz), 4.82-4.90 (1H, m), 6.67 (1H, d, J = 7.8 Hz), 6.75 (1H, d, J = 7.8 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.17 (2H, d, J = 9.0 Hz).

[0060]

Reference Example 15

20 3-(4-Isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran

Using 2-(2-hydroxy-1-(4-isopropylphenyl)ethyl)-3,5-dimethylphenol synthesized in Reference Example 10, the
title compound was synthesized in the same manner as in
Reference Example 13. Yield 85%. Melting point: 46 - 47°C
25 (methanol).

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, J = 7.0 Hz), 1.92 (3H, s), 2.29 (3H, s), 2.86 (1H, septet, J = 7.0 Hz), 4.35-4.53 (2H, m), 4.75-4.90 (1H, m), 6.47 (1H, s), 6.55 (1H, s), 7.05 (2H, d, J = 8.0 Hz), 7.13 (2H, d, J = 8.0 Hz).

5 [0061]

Reference Example 16

5-Bromo-3-(4-isopropylphenyl)-2,3-dihydro-1-benzofuran

Using 4-bromo-2-(2-hydroxy-1-(4-isopropylphenyl)ethyl)phenol synthesized in Reference
10 Example 11, the title compound was synthesized in the same manner as in Reference Example 13. Yield 62%. Melting point: 90 - 91°C (methanol).

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, J = 6.8 Hz), 2.90 (1H, septet, J = 6.8 Hz), 4.37-4.47 (1H, m), 4.56-4.67 (1H, m), 4.89 (1H, dd, J = 9.6, 8.8 Hz), 6.74 (1H, d, J = 8.4 Hz), 7.07-7.29
15 (6H, m).

[0062]

Reference Example 17

3-(4-Isopropylphenyl)-3,4,6,7-tetramethyl-2,3-dihydro-1-
20 benzofuran

Using 2-(2-hydroxy-1-(4-isopropylphenyl)-1-methylethyl)-3,5,6-trimethylphenol synthesized in Reference Example 12, the title compound was synthesized in the same manner as in Reference Example 13. Yield 95%. Oily matter.
25 ¹H-NMR (CDCl₃) δ: 1.23 (6H, d, J = 6.9 Hz), 1.74 (3H, s),

1.80 (3H, s), 2.15 (3H, s), 2.22 (3H, s), 2.87 (1H, septet, $J = 6.9$ Hz), 4.38 (1H, d, $J = 8.4$ Hz), 4.46 (1H, d, $J = 8.4$ Hz), 6.45 (1H, s), 7.13 (2H, d, $J = 8.4$ Hz), 7.20 (2H, d, $J = 8.4$ Hz).

5 [0063]

Reference Example 18

5-Bromo-3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran

To a mixture of 3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran synthesized in Reference Example 13 (6.10 g, 21.8 mmol) and sodium acetate (1.97 g, 24.0 mmol) in acetonitrile (30 mL) was added bromine (1.17 mL, 22.9 mmol), and the mixture was stirred at the same temperature for 1 hour. Water was poured into the reaction mixture, which was extracted with ethyl acetate. The extract was washed with a saturated sodium hydrogen carbonate solution and water, dried over magnesium sulfate, filtered and then concentrated under reduced pressure. The obtained residue was crystallized from methanol to obtain 7.90 g (yield 99%) of the title compound. Melting point: 86 - 87°C (methanol).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (6H, d, $J = 6.9$ Hz), 2.04 (3H, s), 2.23 (3H, s), 2.38 (3H, s), 2.86 (1H, septet, $J = 6.9$ Hz), 4.41 (1H, dd, $J = 8.4, 4.8$ Hz), 4.54 (1H, dd, $J = 9.0, 4.8$ Hz), 4.81 (1H, t, $J = 9.0$ Hz), 7.01 (2H, d, $J = 8.1$ Hz),

7.12 (2H, d, J = 8.1 Hz).

[0064]

Reference Example 19

5-Bromo-3-(4-isopropylphenyl)-6,7-dimethyl-2,3-dihydro-1-
5 benzofuran

Using 3-(4-isopropylphenyl)-6,7-dimethyl-2,3-dihydro-
1-benzofuran synthesized in Reference Example 14, the title
compound was synthesized in the same manner as in Reference
Example 18. Yield 68%. Melting point: 114 - 115°C
10 (methanol).

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, J = 7.0 Hz), 2.23 (3H, s),
2.33 (3H, s), 2.89 (1H, septet, J = 7.0 Hz), 4.39 (1H, dd,
J = 8.4, 7.8 Hz), 4.54-4.66 (1H, m), 4.86 (1H, dd, J = 9.2,
8.4 Hz), 7.03 (1H, s), 7.11 (2H, d, J = 8.4 Hz), 7.18 (2H,
15 d, J = 8.4 Hz).

[0065]

Reference Example 20

5-Bromo-3-(4-isopropylphenyl)-3,4,6,7-tetramethyl-2,3-
dihydro-1-benzofuran

20 Using 3-(4-isopropylphenyl)-3,4,6,7-tetramethyl-2,3-
dihydro-1-benzofuran synthesized in Reference Example 17,
the title compound was synthesized in the same manner as in
Reference Example 18. Yield 98%. Oily matter.

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, J = 6.9 Hz), 1.74 (3H, s),
25 1.90 (3H, s), 2.23 (3H, s), 2.38 (3H, s), 2.88 (1H, septet,

$J = 6.9$ Hz), 4.37 (1H, d, $J = 8.7$ Hz), 4.42 (1H, d, $J = 8.7$ Hz), 7.14 (2H, d, $J = 8.4$ Hz), 7.19 (2H, d, $J = 8.4$ Hz).

[0066]

Reference Example 21

5 5-Bromo-3-(4-isopropylphenyl)-3,6,7-trimethyl-1-benzofuran-2(3H)-one

Using 3-(4-isopropylphenyl)-3,6,7-trimethyl-1-benzofuran-2(3H)-one synthesized in Reference Example 7, the title compound was synthesized in the same manner as in
10 Reference Example 18. Yield 73%. Melting point: 116 - 117°C (methanol).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (6H, d, $J = 6.9$ Hz), 1.86 (3H, s), 2.34 (3H, s), 2.41 (3H, s), 2.88 (1H, septet, $J = 6.9$ Hz), 7.15-7.25 (5H, m).

15 [0067]

Reference Example 22

4-Bromo-6-(2-hydroxy-1-(4-isopropylphenyl)-1-methylethyl)-2,3-dimethylphenol

Using 5-bromo-3-(4-isopropylphenyl)-3,6,7-trimethyl-1-benzofuran-2(3H)-one synthesized in Reference Example 21, the title compound was synthesized in the same manner as in
20 Reference Example 8. Yield 83%. Melting point: 110 - 111°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, d, $J = 6.9$ Hz), 1.58 (3H, s),
25 2.15 (3H, s), 2.37 (3H, s), 2.89 (1H, septet, $J = 6.9$ Hz),

3.99 (1H, d, J = 11.7 Hz), 4.23 (1H, d, J = 11.7 Hz), 6.27 (1H, br s), 7.19 (4H, s), 7.40 (1H, s), 1H unidentified.

[0068]

Reference Example 23

5 5-Bromo-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran

To a solution of 3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran synthesized in Reference Example 15 (5.62 g, 21.1 mmol) in acetonitrile (60 mL) was added N-bromosuccinimide (3.76 g, 21.1 mmol) at 0°C, and the mixture was stirred at the same temperature for 1 hour. The solvent was distilled off under reduced pressure to obtain a residue, which was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to obtain 15 5.95 g (yield 82%) of the title compound. Melting point: 90 - 91°C (methanol).

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, J = 6.9 Hz), 2.05 (3H, s), 2.39 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 4.41 (1H, dd, J = 8.4, 4.5 Hz), 4.52 (1H, dd, J = 9.0, 4.5 Hz), 4.78-4.86 20 (1H, m), 6.66 (1H, s), 7.01 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz).

[0069]

Reference Example 24

N-Benzyl-3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine 25

To a solution of 5-bromo-3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran obtained in Reference Example 18 (920 mg, 2.56 mmol) and benzylamine (0.34 mL, 3.07 mmol) in toluene (10 mL), were added palladium acetate (6 mg, 0.03 mmol) and BINAP (48 mg, 0.09 mmol) at room temperature, and the mixture was stirred under argon stream for 15 minutes. Sodium tert-butoxide (344 mg, 3.58 mmol) was added to the reaction solution at room temperature, and then the mixture was heated under reflux for 18 hours.

Water was added to the reaction solution, which was extracted with ethyl acetate, the organic layer was washed with water and a saturated brine and then was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 50 : 1) to obtain 900 mg (yield 91%) of the title compound as an oily matter. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (6H, d, $J = 6.9$ Hz), 1.87 (3H, s), 2.20 (3H, s), 2.27 (3H, s), 2.67-3.02 (2H, m), 3.91 (2H, s), 4.38 (1H, dd, $J = 8.4, 4.8$ Hz), 4.52 (1H, dd, $J = 9.0, 4.8$ Hz), 4.80 (1H, t, $J = 9.0$ Hz), 7.03 (2H, d, $J = 8.1$ Hz), 7.12 (2H, d, $J = 8.1$ Hz), 7.20-7.42 (5H, m).

[0070]

Reference Example 25

N-Benzyl-3-(4-isopropylphenyl)-6,7-dimethyl-2,3-dihydro-1-

benzofuran-5-amine

Using 5-bromo-3-(4-isopropylphenyl)-6,7-dimethyl-2,3-dihydro-1-benzofuran synthesized in Reference Example 19, the title compound was synthesized in the same manner as in
5 Reference Example 24. Yield 85%. Melting point: 108 - 109°C (methanol).

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, J = 6.9 Hz), 2.08 (3H, s), 2.22 (3H, s), 2.88 (1H, septet, J = 7.0 Hz), 3.42 (1H, br s), 4.18 (2H, s), 4.28 (1H, t, J = 7.5 Hz), 4.55-4.64 (1H, m),
10 4.79 (1H, t, J = 9.0 Hz), 6.30 (1H, s), 7.11 (2H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.21 - 7.37 (5H, m).

[0071]

Reference Example 26

N-Benzyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-
15 benzofuran-5-amine

Using 5-bromo-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran synthesized in Reference Example 23, the title compound was synthesized in the same manner as in
Reference Example 24. Yield 99%. Melting point: 82 - 83°C
20 (methanol).

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, J = 6.9 Hz), 1.90 (3H, s), 2.27 (3H, s), 2.67-3.02 (2H, m), 3.93 (2H, s), 4.38 (1H, dd, J = 8.4, 4.5 Hz), 4.49 (1H, dd, J = 9.0, 4.5 Hz), 4.75-4.83 (1H, m), 6.59 (1H, s), 7.02 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J = 8.1 Hz), 7.19-7.39 (5H, m).
25

[0072]

Reference Example 27

N-Benzyl-3-(4-isopropylphenyl)-2,3-dihydro-1-benzofuran-5-amine

5 Using 5-bromo-3-(4-isopropylphenyl)-2,3-dihydro-1-benzofuran synthesized in Reference Example 16, the title compound was synthesized in the same manner as in Reference Example 24. Yield 89%. Oily matter.

10 ¹H-NMR (CDCl₃) δ: 1.24 (6H, d, J = 6.9 Hz), 2.88 (1H, septet, J = 6.9 Hz), 3.42 (1H, br s), 4.20 (2H, s), 4.31 (1H, dd, J = 8.7, 7.8 Hz), 4.51-4.59 (1H, m), 4.80 (1H, dd, J = 9.0, 8.7 Hz), 6.38 (1H, d, J = 2.4 Hz), 6.46 (1H, dd, J = 8.1, 2.4 Hz), 6.71 (1H, d, J = 8.1 Hz), 7.08-7.37 (9H, m).

[0073]

15 Reference Example 28

N-Benzyl-3-(4-isopropylphenyl)-3,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-amine

20 Using 5-bromo-3-(4-isopropylphenyl)-3,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran synthesized in Reference Example 20, the title compound was synthesized in the same manner as in Reference Example 24. Yield 25%. Oily matter.

25 ¹H-NMR (CDCl₃) δ: 1.23 (6H, d, J = 6.9 Hz), 1.73 (3H, s), 1.74 (3H, s), 2.20 (3H, s), 2.27 (3H, s), 2.78-3.10 (2H, m), 3.88 (1H, d, J = 13.2 Hz), 3.93 (1H, d, J = 13.2 Hz), 4.35

(1H, d, J = 8.4 Hz), 4.39 (1H, d, J = 8.4 Hz), 7.10-7.38 (9H, m).

[0074]

Reference Example 29

5 N-Benzyl-3-(4-isopropylphenyl)-3,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine

To a solution of 4-bromo-6-(2-hydroxy-1-(4-isopropylphenyl)-1-methylethyl)-2,3-dimethylphenol obtained in Reference Example 22 (830 mg, 2.21 mmol) and
10 triphenylphosphine (638 mg, 2.43 mmol) in THF (60 mL) was added diethyl azodicarboxylate (a 40% toluene solution, 1.06 g, 2.43 mmol) with ice-cooling, and the mixture was stirred at room temperature for 1 hour. The solvent was concentrated under reduced pressure to obtain a residue,
15 which was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to obtain oily 5-bromo-3-(4-isopropylphenyl)-3,6,7-trimethyl-2,3-dihydro-1-benzofuran 660 mg. To a solution of said compound (660 mg, 1.84 mmol) and benzylamine (0.24 mL, 2.21 mmol) in toluene
20 (10 mL) were added palladium acetate (4 mg, 0.02 mmol) and BINAP (34 mg, 0.6 mmol) at room temperature, and the mixture was stirred under argon stream for 15 minutes. Sodium tert-butoxide (248 mg, 2.58 mmol) was added to the reaction solution at room temperature, and the mixture was
25 heated under argon stream for 18 hours. Water was added to

the reaction solution, which was extracted with ethyl acetate, the organic layer was washed with water and a saturated brine and then was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 50 : 1), to obtain 660 mg (yield 77%) of the title compound as an oily matter.

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, J = 7.0 Hz), 1.69 (3H, s), 2.09 (3H, s), 2.22 (3H, s), 2.87 (1H, septet, J = 7.0 Hz), 3.47 (1H, br s), 4.23 (2H, s), 4.35 (1H, d, J = 8.4 Hz), 4.48 (1H, d, J = 8.4 Hz), 6.32 (1H, s), 7.07 - 7.42 (9H, m).

[0075]

Reference Example 30

3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine

A mixture of N-benzyl-3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 24 (900 mg, 2.33 mmol), 10% - palladium carbon (50% hydrous, 90 mg) and ammonium formate (294 mg, 4.66 mmol) in ethanol (10 mL) was heated under reflux for 2 hours. The solid material was removed and the filtrate was concentrated under reduced pressure. Water and ethyl acetate were added to the residue to separate the organic layer, and the aqueous layer was extracted with ethyl

acetate. The combined organic layer was washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain a residue, which was crystallized from ethyl acetate - hexane to
5 obtain 510 mg (yield 74%) of the title compound. Melting point: 171 - 173°C.

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, J = 6.9 Hz), 1.84 (3H, s), 2.11 (3H, s), 2.20 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.26 (2H, br s), 4.30-4.41 (1H, m), 4.47-4.60 (1H, m),
10 4.70-4.82 (1H, m), 7.05 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J = 8.1 Hz).

[0076]

Reference Example 31

3-(4-Isopropylphenyl)-6,7-dimethyl-2,3-dihydro-1-
15 benzofuran-5-amine

Using N-benzyl-3-(4-isopropylphenyl)-6,7-dimethyl-2,3-dihydro-1-benzofuran-5-amine synthesized in Reference Example 25, the title compound was synthesized in the same manner as in Reference Example 30. Yield 88%. Oily matter.

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, J = 6.9 Hz), 2.00 (2H, br s), 2.08 (3H, s), 2.20 (3H, s), 2.88 (1H, septet, J = 6.9 Hz), 4.31 (1H, t, J = 7.8 Hz), 4.56 (1H, t, J = 7.8 Hz), 4.75-4.83 (1H, m), 6.29 (1H, s), 7.14 (2H, d, J = 9.0 Hz), 7.17 (2H, d, J = 9.0 Hz).

25 [0077]

Reference Example 32

3-(4-Isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-amine

Using N-benzyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-amine synthesized in Reference Example 26, the title compound was synthesized in the same manner as in Reference Example 30. Yield 72%. Melting point: 81 - 82°C.

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, J = 6.9 Hz), 1.85 (3H, s), 2.18 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.07 (2H, br s), 4.35 (1H, dd, J = 8.4, 4.5 Hz), 4.49 (1H, dd, J = 9.0, 4.5 Hz), 4.71-4.80 (1H, m), 6.54 (1H, s), 7.03 (2H, d, J = 8.1 Hz), 7.11 (2H, d, J = 8.1 Hz).

[0078]

Reference Example 33

3-(4-Isopropylphenyl)-2,3-dihydro-1-benzofuran-5-amine

Using N-benzyl-3-(4-isopropylphenyl)-2,3-dihydro-1-benzofuran-5-amine synthesized in Reference Example 27, the title compound was synthesized in the same manner as in Reference Example 30. Yield 77%. Oily matter.

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, J = 6.9 Hz), 2.88 (1H, septet, J = 6.9 Hz), 3.32 (2H, br s), 4.32 (1H, dd, J = 8.7, 7.5 Hz), 4.49-4.57 (1H, m), 4.80 (1H, dd, J = 9.0, 8.7 Hz), 6.38 (1H, d, J = 2.4 Hz), 6.49 (1H, dd, J = 8.1, 2.4 Hz), 6.67 (1H, d, J = 8.1 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.16 (2H,

d, $J = 8.4$ Hz).

[0079]

Reference Example 34

3-(4-Isopropylphenyl)-3,4,6,7-tetramethyl-2,3-dihydro-1-
5 benzofuran-5-amine

Using N-benzyl-3-(4-isopropylphenyl)-3,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-amine synthesized in Reference Example 28, the title compound was synthesized in the same manner as in Reference Example 30. Yield 79%.

10 Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (6H, d, $J = 6.9$ Hz), 1.69 (3H, s),
1.77 (3H, s), 2.15 (3H, s), 2.20 (3H, s), 2.85 (1H, septet,
 $J = 6.9$ Hz), 3.10 (2H, br s), 4.30 (1H, d, $J = 8.4$ Hz),
4.34 (1H, d, $J = 8.4$ Hz), 7.12 (2H, d, $J = 8.4$ Hz), 7.22 (2H,
15 d, $J = 8.4$ Hz).

[0080]

Reference Example 35

3-(4-Isopropylphenyl)-3,6,7-trimethyl-2,3-dihydro-1-
benzofuran-5-amine

20 Using N-benzyl-3-(4-isopropylphenyl)-3,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine synthesized in Reference Example 29, the title compound was synthesized in the same manner as in Reference Example 30. Yield 71%. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (6H, d, $J = 6.9$ Hz), 1.69 (3H, s),
25 2.09 (3H, s), 2.20 (3H, s), 2.87 (1H, septet, $J = 6.9$ Hz),

3.30 (2H, br s), 4.35 (1H, d, $J = 8.7$ Hz), 4.50 (1H, d, $J = 8.7$ Hz), 6.29 (1H, s), 7.14 (2H, d, $J = 8.1$ Hz), 7.23 (2H, d, $J = 8.1$ Hz).

[0081]

5 Reference Example 36

2-(2,3-Dimethylphenoxy)-2-methylpropionic acid

To a solution of 2,3-dimethylphenol (25.0 g, 205 mmol) in dimethylsulfoxide (200 mL) were added ethyl 2-bromo-isobutyrate (60 mL, 409 mmol) and potassium carbonate (56.5 g, 409 mmol) at room temperature, and the mixture was stirred for 36 hours. Water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with water and a saturated brine, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure to obtain crude oily ethyl 2-(2,3-dimethylphenoxy)-2-methylpropionate. 12 N Aqueous sodium hydroxide solution (20 mL, 240 mmol) was added to the mixed solution of this compound in THF (160 mL) and methanol (40 mL) at room temperature, stirred for 12 hours, and then concentrated under reduced pressure. Water and hydrochloric acid were added to the reaction solution to acidity the aqueous layer, which was extracted with ethyl acetate. The organic layer was washed with water and a saturated brine and then was dried over anhydrous sodium sulfate. The solvent was distilled off

under reduced pressure to obtain a residue, which was crystallized from ethyl acetate - hexane to obtain 21.3 g (yield 50%) of the title compound. Melting point: 71 - 73°C.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.60 (6H, s), 2.16 (3H, s), 2.27 (3H, s), 6.72 (1H, d, $J = 7.8$ Hz), 6.88 (1H, d, $J = 7.5$ Hz), 7.00 (1H, 7, $J = 7.8$ Hz), 1H unidentified.

[0082]

Reference Example 37

10 2-(3,5-Dimethylphenoxy)-2-methylpropionic acid

Using 3,5-dimethylphenol, the title compound was synthesized in the same manner as in Reference Example 36. Yield 96%. Oily matter.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.59 (6H, s), 2.27 (6H, s), 6.56 (1H, s), 6.72 (1H, s).

[0083]

Reference Example 38

2-(2,5-Dimethylphenoxy)-2-methylpropionic acid

20 Using 2,5-dimethylphenol, the title compound was synthesized in the same manner as in Reference Example 36. Yield 57%. Melting point: 107 - 109°C (ethyl acetate - hexane).

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.62 (6H, s), 2.20 (3H, s), 2.27 (3H, s), 6.64 (1H, s), 6.77 (1H, d, $J = 7.5$ Hz), 7.05 (1H, d, $J = 7.5$ Hz), 9.50 (1H, br s).

[0084]

Reference Example 39

2-(2,3,5-Trimethyl phenoxy)-2-methylpropionic acid

Using 2,3,5-trimethylphenol, the title compound was
5 synthesized in the same manner as in Reference Example 36.
Yield 65%. Melting point: 91 - 94°C (ethyl acetate -
hexane).

¹H-NMR (CDCl₃) δ: 1.59 (6H, s), 2.12 (3H, s), 2.22 (3H, s),
2.23 (3H, s), 6.53 (1H, s), 6.71 (1H, s), 1H unidentified.

10 [0085]

Reference Example 40

2-(3,4,5-Trimethyl phenoxy)-2-methylpropionic acid

Using 3,4,5-trimethylphenol, the title compound was
synthesized in the same manner as in Reference Example 36.
15 Yield 57%. Melting point: 77 - 78°C (hexane).

¹H-NMR (CDCl₃) δ: 1.56 (6H, s), 2.11 (3H, s), 2.24 (6H, s),
6.61 (2H, s), 1H unidentified.

[0086]

Reference Example 41

20 2,2,6,7-Tetramethyl-1-benzofuran-3(2H)-one

To a solution of 2-(2,3-dimethylphenoxy)-2-
methylpropionic acid obtained in Reference Example 36 (21.0
g, 101 mmol) in THF (200 mL) was added DMF (0.1 mL), and
then to the mixture was added dropwise oxalyl chloride
25 (10.6 mL, 121 mmol). The reaction solution was warmed to

room temperature, stirred for 1 hour, and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (200 mL), to which was added aluminum chloride (32.3 g, 242 mmol) at -70°C or lower, and then warmed to room temperature over 12 hours. The reaction solution was added to water with ice-cooling and dichloromethane was distilled off under reduced pressure, which was extracted with ethyl acetate. The organic layer was washed with water, a saturated sodium hydrogen carbonate solution, water and a saturated brine, and then was dried over anhydrous sodium sulfate. The residue after distilling off the solvent under reduced pressure was crystallized from ethyl acetate - hexane to obtain 17.5 g (yield 71%) of the title compound. Melting point: 79 - 81°C (methanol).

¹H-NMR (CDCl₃) δ: 1.46 (6H, s), 2.21 (3H, s), 2.35 (3H, s), 6.88 (1H, d, J = 8.0 Hz), 7.40 (1H, d, J = 8.0 Hz).

[0087]

Reference Example 42

2,2,4,6-Tetramethyl-1-benzofuran-3(2H)-one

Using 2-(3,5-dimethylphenoxy)-2-methylpropionic acid obtained in Reference Example 37, the title compound was synthesized in the same manner as in Reference Example 41. Yield 92%. Oily matter.

¹H-NMR (CDCl₃) δ: 1.43 (6H, s), 2.37 (3H, s), 2.54 (3H, s),

6.62 (1H, s), 6.66 (1H, s).

[0088]

Reference Example 43

2,2,4,7-Tetramethyl-1-benzofuran-3(2H)-one

5 Using 2-(2,5-dimethylphenoxy)-2-methylpropionic acid
obtained in Reference Example 38, the title compound was
synthesized in the same manner as in Reference Example 41.
Yield 97%. Oily matter.

¹H-NMR (CDCl₃) δ: 1.45 (6H, s), 2.25 (3H, s), 2.55 (3H, s),
10 6.70 (1H, d, J = 7.5 Hz), 7.26 (1H, d, J = 7.5 Hz).

[0089]

Reference Example 44

2,2,4,6,7-Pentamethyl-2,3-dihydro-1-benzofuran-3(2H)-one

15 Using 2-(2,3,5-trimethyl phenoxy)-2-methylpropionic
acid obtained in Reference Example 39, the title compound
was synthesized in the same manner as in Reference Example
41. Yield 33%. Melting point: 99 - 101°C (hexane).

¹H-NMR (CDCl₃) δ: 1.44 (6H, s), 2.16 (3H, s), 2.30 (3H, s),
2.52 (3H, s), 6.63 (1H, s).

20 [0090]

Reference Example 45

2,2,4,5,6-Pentamethyl-1-benzofuran-3(2H)-one

25 Using 2-(3,4,5-trimethyl phenoxy)-2-methylpropionic
acid obtained in Reference Example 40, the title compound
was synthesized in the same manner as in Reference Example

41. Yield 90%. Melting point: 77 - 78°C (hexane).

¹H-NMR (CDCl₃) δ: 1.42 (6H, s), 2.14 (3H, s), 2.34 (3H, s), 2.57 (3H, s), 6.73 (1H, s).

[0091]

5 Reference Example 46

2,2,6,7-Tetramethyl-5-nitro-1-benzofuran-3(2H)-one

To a solution of 2,2,6,7-tetramethyl-1-benzofuran-3(2H)-one obtained in Reference Example 41 (5.20 g, 27.3 mmol) in anhydrous trifluoroacetic acid (50 mL) and
10 chloroform (5 mL) was added ammonium nitrate (2.10 g, 32.8 mmol) at 0°C, and the mixture was stirred at the same temperature for 2 hours, and then concentrated under reduced pressure. Water was added to the residue, which was extracted with ethyl acetate. The extract was washed
15 with water and a saturated sodium hydrogen carbonate solution, and then was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain a residue, which was purified by silica gel column chromatography (hexane : ethyl acetate = 50 : 1) to obtain
20 5.40 g (yield 84%) of the title compound. Melting point: 131 - 132°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.50 (6H, s), 2.32 (3H, s), 2.52 (3H, s), 8.08 (1H, s).

[0092]

25 Reference Example 47

2,2,4,7-Tetramethyl-5-nitro-1-benzofuran-3(2H)-one

Using 2,2,4,7-tetramethyl-1-benzofuran-3(2H)-one obtained in Reference Example 43, the title compound was synthesized in the same manner as in Reference Example 46.

5 Yield 46%. Melting point: 124 - 126°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.50 (6H, s), 2.32 (3H, s), 2.87 (3H, s), 8.11 (1H, s).

[0093]

10 Reference Example 48

5-Bromo-2,2,4,6-tetramethyl-1-benzofuran-3(2H)-one

Using 2,2,4,6-tetramethyl-1-benzofuran-3(2H)-one obtained in Reference Example 42, the title compound was synthesized in the same manner as in Reference Example 18.

15 Yield 73%. Melting point: 63 - 64°C (methanol).

¹H-NMR (CDCl₃) δ: 1.44 (6H, s), 2.48 (3H, s), 2.68 (3H, s), 6.83 (1H, s).

[0094]

Reference Example 49

20 5-Bromo-2,2,4,6,7-pentamethyl-1-benzofuran-3(2H)-one

Using 2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-3(2H)-one obtained in Reference Example 44, the title compound was synthesized in the same manner as in Reference Example 18. Yield 73%. Melting point: 92 - 93°C

25 (methanol).

¹H-NMR (CDCl₃) δ: 1.44 (6H, s), 2.26 (3H, s), 2.47 (3H, s), 2.66 (3H, s).

[0095]

Reference Example 50

5 7-Bromo-2,2,4,5,6-pentamethyl-1-benzofuran-3(2H)-one

Using 2,2,4,5,6-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 45, the title compound was synthesized in the same manner as in Reference Example 18. Yield 79%. Melting point: 145 - 146°C (methanol).

10 ¹H-NMR (CDCl₃) δ: 1.49 (6H, s), 2.23 (3H, s), 2.49 (3H, s), 2.55 (3H, s).

[0096]

Reference Example 51

5-(Benzylamino)-2,2,4,6-tetramethyl-1-benzofuran-3(2H)-one

15 Using 5-bromo-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-3(2H)-one obtained in Reference Example 48, the title compound was synthesized in the same manner as in Reference Example 24. Yield 75%. Oily matter.

20 ¹H-NMR (CDCl₃) δ: 1.43 (6H, s), 2.35 (3H, s), 2.54 (3H, s), 3.02 (1H, br s), 3.99 (2H, s), 6.73 (1H, s), 7.24-7.42 (5H, m).

[0097]

Reference Example 52

25 5-(Benzylamino)-2,2,4,6,7-pentamethyl-1-benzofuran-3(2H)-one

Using 5-bromo-2,2,4,6,7-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 49, the title compound was synthesized in the same manner as in Reference Example 24. Yield 88%. Melting point: 98 - 99°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.43 (6H, s), 2.21 (3H, s), 2.35 (3H, s), 2.50 (3H, s), 3.04 (1H, br s), 3.94 (2H, s), 7.26-7.41 (5H, m).

[0098]

Reference Example 53

7-(Benzylamino)-2,2,4,5,6-pentamethyl-1-benzofuran-3(2H)-one

Using 7-bromo-2,2,4,5,6-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 50, the title compound was synthesized in the same manner as in Reference Example 24. Yield 72%. Melting point: 108 - 109°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.38 (6H, s), 2.14 (3H, s), 2.28 (3H, s), 2.51 (3H, s), 3.61 (1H, br s), 4.27 (2H, s), 7.19-7.37 (5H, m).

[0099]

Reference Example 54

5-Amino-2,2,6,7-tetramethyl-1-benzofuran-3(2H)-one

A mixture of 2,2,6,7-tetramethyl-5-nitro-1-benzofuran-3(2H)-one obtained in Reference Example 46 (5.0 g, 21.3

mmol), 10% - palladium carbon (50% hydrous, 500 mg) and ammonium formate (7.06 g, 85.0 mmol) in methanol (100 mL) was heated under reflux for two hours. The solid material was removed and the filtrate was concentrated under reduced pressure. Water and ethyl acetate were added to the residue to separate the organic layer, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The solvent was distilled off under reduced pressure to obtain a residue, which was crystallized with ethyl acetate - hexane to obtain 4.0 g (yield 92%) of the title compound. Melting point: 149 - 150°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.43 (6H, s), 2.19 (3H, s), 2.24 (3H, s), 3.50 (2H, br s), 6.78 (1H, s).

[0100]

Reference Example 55

5-Amino-2,2,4,6-tetramethyl-1-benzofuran-3(2H)-one

Using 5-(benzylamino)-2,2,4,6-tetramethyl-1-benzofuran-3(2H)-one obtained in Reference Example 51, the title compound was synthesized in the same manner as in Reference Example 30. Yield 95%. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.43 (6H, s), 2.19 (3H, s), 2.24 (3H, s), 3.50 (2H, br s), 6.78 (1H, s).

[0101]

Reference Example 56

5-Amino-2,2,4,7-tetramethyl-1-benzofuran-3(2H)-one

Using 2,2,4,7-tetramethyl-5-nitro-1-benzofuran-3(2H)-one obtained in Reference Example 47, the title compound was synthesized in the same manner as in Reference Example 54. Yield 97%. Melting point: 124 - 126°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.42 (6H, s), 2.21 (3H, s), 2.40 (3H, s), 3.40 (2H, br s), 6.82 (1H, s).

10 [0102]

Reference Example 57

5-Amino-2,2,4,6,7-pentamethyl-1-benzofuran-3(2H)-one

Using 5-(benzylamino)-2,2,4,6,7-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 52, the title compound was synthesized in the same manner as in Reference Example 30. Yield 88%. Melting point: 92 - 93°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.41 (6H, s), 2.19 (3H, s), 2.21 (3H, s), 2.45 (3H, s), 3.44 (2H, br s).

20 [0103]

Reference Example 58

7-Amino-2,2,4,5,6-pentamethyl-1-benzofuran-3(2H)-one

Using 7-(benzylamino)-2,2,4,5,6-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 53, the title compound was synthesized in the same manner as in

25

Reference Example 30. Yield: quantitative. Melting point:
141 - 142°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.44 (6H, s), 2.16 (3H, s), 2.19 (3H, s),
2.50 (3H, s), 3.59 (2H, br s).

5 [0104]

Reference Example 59

tert-Butyl (2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-
benzofuran-5-yl)carbamate

A solution of 5-amino-2,2,6,7-tetramethyl-1-
10 benzofuran-3(2H)-one obtained in Reference Example 54 (3.89
g, 19.5 mmol) and dicarbonic acid ditert-butyl (6.73 mL,
29.3 mmol) in THF (50 mL) was heated under reflux for 16
hours. Water was added to the residue to separate the
organic layer, and the aqueous layer was extracted with
15 ethyl acetate. The combined organic layer was washed with
water, dried over anhydrous sodium sulfate and then
concentrated under reduced pressure. The obtained residue
was crystallized with hexane - ethyl acetate to obtain 4.80
g (yield 81%) of the title compound. Melting point: 154 -
20 155°C.

¹H-NMR (CDCl₃) δ: 1.44 (6H, s), 1.50 (9H, s), 2.24 (3H, s),
2.25 (3H, s), 6.12 (1H, br s), 7.58 (1H, s).

[0105]

Reference Example 60

25 tert-Butyl (2,2,4,6-tetramethyl-3-oxo-2,3-dihydro-1-

benzofuran-5-yl) carbamate

Using 5-amino-2,2,4,6-tetramethyl-1-benzofuran-3(2H)-one obtained in Reference Example 55, the title compound was synthesized in the same manner as in Reference Example 59. Yield 71%. Melting point: 156 - 157°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.44 (6H, s), 1.50 (9H, s), 2.24 (3H, s), 2.25 (3H, s), 6.12 (1H, br s), 7.58 (1H, s).

[0106]

10 Reference Example 61

tert-Butyl (2,2,4,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl) carbamate

Using 5-amino-2,2,4,7-tetramethyl-1-benzofuran-3(2H)-one obtained in Reference Example 56, the title compound was synthesized in the same manner as in Reference Example 59. Yield 96%. Melting point: 144 - 145°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.43 (6H, s), 1.51 (9H, s), 2.25 (3H, s), 2.47 (3H, s), 6.11 (1H, br s), 7.66 (1H, s).

20 [0107]

Reference Example 62

tert-Butyl (2,2,4,6,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl) carbamate

Using 5-amino-2,2,4,6,7-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 57, the title

compound was synthesized in the same manner as in Reference Example 59. Yield 90%. Melting point: 105 - 106°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.42 (6H, s), 1.51 (9H, s), 2.19 (3H, s),
5 2.25 (3H, s), 2.49 (3H, s), 5.81 (1H, br s).

[0108]

Reference Example 63

3,3-Dimethyl-N-(2,2,4,6,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide

10 To a solution of 5-amino-2,2,4,6,7-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 57 (3.00 g, 13.7 mmol) and tert-butylacetyl chloride (2.03 g, 15.1 mmol) in dichloromethane (30 mL) was added triethylamine (2.3 mL, 16.4 mmol) at room temperature, and the mixture
15 was stirred at room temperature for 30 minutes. Water was added to the residue to separate the organic layer, and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with 1 N hydrochloric acid and a saturated sodium hydrogen carbonate solution,
20 dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was crystallized from ethyl acetate - hexane to obtain the targeted product 2.34 g (yield 54%). Melting point: 155 - 156°C.

25 ¹H-NMR (CDCl₃) δ: 1.15 (9H, s), 1.43 (6H, s), 2.19 (3H, s),

2.22 (3H, s), 2.32 (2H, s), 2.47 (3H, s), 6.62 (1H, br s).

[0109]

Reference Example 64

3,3-Dimethyl-N-(2,2,4,5,6-pentamethyl-3-oxo-2,3-dihydro-1-
5 benzofuran-7-yl)butanamide

Using 7-amino-2,2,4,5,6-pentamethyl-1-benzofuran-
3(2H)-one obtained in Reference Example 58, the title
compound was synthesized in the same manner as in Reference
Example 63. Yield 76%. Melting point: 158 - 159°C (ethyl
10 acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.15 (9H, s), 1.40 (6H, s), 2.16 (3H, s),
2.24 (3H, s), 2.32 (2H, s), 2.54 (3H, s), 6.78 (1H, br s).

[0110]

Reference Example 65

15 3,3-Dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-
benzofuran-5-yl)butanamide

Using 5-amino-2,2,6,7-tetramethyl-1-benzofuran-3(2H)-
one obtained in Reference Example 54, the title compound
was synthesized in the same manner as in Reference Example
20 63. Yield 88%. Melting point: 175 - 176°C (ethyl acetate
- hexane).

¹H-NMR (CDCl₃) δ: 1.13 (9H, s), 1.44 (6H, s), 2.24-2.26 (8H,
m), 6.84 (1H, br s), 7.50 (1H, s).

[0111]

25 Reference Example 66

N-(3-Hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of 3,3-dimethyl-N-(2,2,4,6,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide
5 obtained in Reference Example 63 (1.0 g, 3.15 mmol) in methanol was added sodium borohydride (238 mg, 6.30 mmol) at room temperature, and stirred for 1 hour. The reaction solution was concentrated under reduced pressure, and the residue was extracted with ethyl acetate. The organic layer
10 was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was crystallized from ethyl acetate to give the title compound 950 mg (yield 94%). Melting point: 204 - 206°C.

15 ¹H-NMR (CDCl₃) δ: 1.15 (9H, s), 1.29 (3H, s), 1.49 (3H, s), 2.09 (3H, s), 2.11 (3H, s), 2.23 (3H, s), 2.30 (2H, s), 4.70 (1H, d, J = 9.2 Hz), 6.61 (1H, brs), 1H unidentified.

[0112]

Reference Example 67

20 N-(3-Hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65, the title compound was synthesized in the same
25 manner as in Reference Example 66. Yield 92%. Melting

point: 184 - 185°C (THF - hexane).

¹H-NMR (CDCl₃) δ: 1.13 (9H, s), 1.32 (3H, s), 1.48 (3H, s), 1.81 (1H, brs), 2.13 (6H, s), 2.25 (2H, s), 4.73 (1H, brs), 6.79 (1H, brs), 7.34 (1H, s).

5 [0113]

Reference Example 68

tert-Butyl (7-bromo-2,2,4,6-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl) carbamate

To a solution of tert-butyl (2,2,4,6-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl) carbamate obtained in
10 Reference Example 60 (4.86 g, 15.9 mmol) in acetonitrile (70 mL) was added N-bromosuccinimide (5.67 g, 31.8 mmol) was heated under reflux for 1.5 hours. The reaction solution was cooled to room temperature, followed by
15 addition of water, which was extracted with ethyl acetate, and the organic layer was washed with water and a saturation brine, dried over anhydrous sodium sulfate, and then was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl
20 acetate - hexane = 5 : 95 - 30 : 70), and then was recrystallized with ethyl acetate - hexane to obtain 4.40 g (yield 72%) of the title compound. Melting point: 131 - 132°C.

¹H-NMR (CDCl₃) δ: 1.33-1.55 (15H, m), 2.46 (3H, s), 2.49
25 (3H, s), 5.87 (1H, br s).

[0114]

Reference Example 69

tert-Butyl (7-bromo-3-hydroxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate

- 5 Using tert-Butyl (7-bromo-2,2,4,6-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 68, the title compound was synthesized in the same manner as in Reference Example 66. Yield 98%. Melting point: 187 - 188°C (ethyl acetate - hexane).
- 10 ¹H-NMR (CDCl₃) δ: 1.28-1.71 (15H, m), 1.70 (1H, brs), 2.26 (3H, s), 2.34 (3H, s), 4.80 (1H, d, J=9.0Hz), 5.84 (1H, brs).

[0115]

Reference Example 70

3-Bromo-2,4,5-trimethylbenzaldehyde

- 15 To a solution of 2,4,5-trimethylbenzaldehyde (21.3 g, 144 mmol) in dichloromethane (200 mL) was added aluminum chloride (48.0 g, 360 mmol) with ice-cooling, and the mixture was warmed to room temperature. Bromine (7.80 mL, 151 mmol) was added dropwise to the reaction solution at
- 20 room temperature, the mixture was stirred for 4 hours, water was added to the reaction solution, and dichloromethane was distilled off under reduced pressure. The residue was extracted with ethyl acetate and the organic layer was washed with water, a saturated sodium
- 25 hydrogen carbonate solution, 5% sodium sulfite aqueous

solution, water and a saturated brine. The organic layer was dried over anhydrous sodium sulfate and then was concentrated under reduced pressure to obtain 32.5 g (yield 100%) of the title compound. Melting point: 108 - 110°C.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.38 (3H, s), 2.46 (3H, s), 2.73 (3H, s), 7.54 (1H, s), 10.21 (1H, s).

[0116]

Reference Example 71

3-Bromo-2,4,5-trimethylphenol

10 To a solution of 3-bromo-2,4,5-trimethylbenzaldehyde obtained in Reference Example 70 (32.0 g, 141 mmol) in THF (100 mL) was added methanol (200 mL) with ice-cooling, followed by addition of p-toluenesulfonic acid monohydrate (5.40 g, 28.4 mmol) with ice-cooling. Hydrogen peroxide
15 (30%, 24.0 g, 212 mmol) was added dropwise to the reaction solution at 10°C or lower, and the mixture was warmed to room temperature and stirred for 12 hours. Then the reaction solution was stirred at 50°C for 36 hours, followed by addition of an aqueous sodium sulfite solution,
20 and methanol and THF were distilled off under reduced pressure. The residue was extracted with ethyl acetate, the organic layer was washed with water and a saturated brine, and then was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to
25 obtain a residue, which was purified by silica gel column

chromatography (hexane - hexane : ethyl acetate = 10 : 1)
to obtain 9.1 g (yield 30%) of the title compound. Melting
point: 86 - 88°C.

¹H-NMR (CDCl₃) δ: 2.25 (3H, s), 2.30 (3H, s), 2.32 (3H, s),
5 4.63 (1H, s), 6.56 (1H, s).

[0117]

Reference Example 72

2-(3-Bromo-2,4,5-trimethylphenoxy)-2-methylpropionic acid

Using 3-bromo-2,4,5-trimethylphenol obtained in

10 Reference Example 71, the title compound was synthesized in
the same manner as in Reference Example 36. Yield 40%.

Melting point: 151 - 153°C (hexane).

¹H-NMR (CDCl₃) δ: 1.59 (6H, s), 2.26 (3H, s), 2.33 (6H, s),
6.67 (1H, s), 9.60 (1H, br s).

15 [0118]

Reference Example 73

6-Bromo-2,2,4,5,7-pentamethyl-1-benzofuran-3(2H)-one

Using 2-(3-bromo-2,4,5-trimethylphenoxy)-2-
methylpropionic acid obtained in Reference Example 72, the
20 title compound was synthesized in the same manner as in
Reference Example 41. Yield 97%. Melting point: 125 -
127°C

¹H-NMR (CDCl₃) δ: 1.44 (6H, s), 2.34 (3H, s), 2.37 (3H, s),
2.60 (3H, s).

25 [0119]

Reference Example 74

6-(Benzylamino)-2,2,4,5,7-pentamethyl-1-benzofuran-3(2H)-one

Using 6-bromo-2,2,4,5,7-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 73, the title compound was synthesized in the same manner as in Reference Example 24. Yield 95%. Melting point: 79 - 83°C.

¹H-NMR (CDCl₃) δ: 1.43 (6H, s), 2.11 (3H, s), 2.16 (3H, s), 2.55 (3H, s), 3.86 (1H, br s), 4.34 (2H, s), 7.26-7.42 (5H, m).

[0120]

Reference Example 75

6-Amino-2,2,4,5,7-pentamethyl-1-benzofuran-3(2H)-one

Using 6-(benzylamino)-2,2,4,5,7-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 74, the title compound was synthesized in the same manner as in Reference Example 30. Yield 87%. Melting point: 150 - 151°C.

¹H-NMR (CDCl₃) δ: 1.41 (6H, s), 2.04 (3H, s), 2.06 (3H, s), 2.55 (3H, s), 4.27 (2H, br s).

[0121]

Reference Example 76

(2,2,4,5,7-Pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-6-yl)formamide

A mixture of formic acid (5 mL) with 6-amino-

2,2,4,5,7-pentamethyl-1-benzofuran-3(2H)-one (700 mg, 3.19 mmol) obtained in Reference Example 75, was heated under reflux for 5 hours. The solvent was distilled off under reduced pressure, water and ethyl acetate were added to the residue, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and a saturated sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The obtained residue was crystallized from hexane - ethyl acetate to obtain 640 mg (yield 81%) of the title compound. Melting point: 191 - 192°C.

¹H-NMR (CDCl₃) δ: 1.40-1.52 (6H, m), 2.00-2.28 (3H, m), 2.56, 2.57 (1.5H x2, s), 2.60 (3H, s), 7.07 (0.5H, br s), 7.20-7.35 (0.5H, m), 8.18 (0.5H, d, J = 11.6 Hz), 8.46 (0.5H, d, J = 1.4 Hz).

[0122]

Reference Example 77

3-(4-Isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-amine hydrochloride

To a solution of 4-bromocumene (6.25 g, 31.4 mmol) in THF (50 mL) was added dropwise a solution of n-butyllithium in hexane (1.60 M, 19.6 mL, 31.4 mmol) under argon atmosphere at -78°C, and the mixture was stirred at the same temperature for 30 minutes. Then, to the reaction solution was added dropwise a solution of tert-butyl

(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 59 (500 mg, 2.02 mmol) in THF (5 mL) at the same temperature, and the reaction solution was stirred at room temperature for 1 hour, followed by addition of water, which was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to obtain oily tert-butyl (3-hydroxy-3-(4-isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate. A mixture of said compound with trifluoroacetic acid (10 mL) was added triethylsilane (1.0 mL, 6.4 mmol) with ice-cooling, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and to the residue was added a saturated sodium hydrogen carbonate solution to alkalify the aqueous layer, which was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to obtain the free salt of the title compound. Then, it was made hydrochloride in a 4 N hydrochloric acid / methanol solution to obtain 2.03

g (yield 37%) of the title compound. Melting point: 166 - 168°C (decomp.) (methanol).

¹H-NMR (DMSO-d₆) δ: 0.90 (3H, s), 1.19 (6H, d, J = 6.8 Hz), 1.51 (3H, s), 2.14 (3H, s), 2.21 (3H, s), 2.87 (1H, septet, J = 6.8 Hz), 4.39 (1H, s), 6.96 (1H, s), 6.97 (2H, d, J = 8.0 Hz), 7.20 (2H, d, J = 8.0 Hz), 10.1 (2H, br s), 1H unidentified.

[0123]

Reference Example 78

10 3-(4-Isopropylphenyl)-2,2,4,7-tetramethyl-2,3-dihydro-1-benzofuran-5-amine hydrochloride

Using tert-butyl (2,2,4,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 61 and 4-bromocumene, the title compound was
15 synthesized in the same manner as in Reference Example 77. Yield 78%. Melting point: 239 - 240°C (decomp.) (methanol).
¹H-NMR (DMSO-d₆) δ: 0.97 (3H, s), 1.17 (6H, d, J = 6.9 Hz), 1.44 (3H, s), 1.85 (3H, s), 2.15 (3H, s), 2.84 (1H, septet, J = 6.9 Hz), 4.29 (1H, s), 6.58-7.27 (5H, m), 9.98 (2H, br
20 s), 1H unidentified.

[0124]

Reference Example 79

3-(4-Tert-butylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine hydrochloride

25 Using tert-butyl (2,2,4,6,7-pentamethyl-3-oxo-2,3-

dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 62 and 4-bromo-tert-butylbenzene, the title compound was synthesized in the same manner as in Reference Example 77. Yield 23%. Melting point: 265 - 267°C

5 (decomp.) (methanol).

¹H-NMR (DMSO-d₆) δ: 0.96 (3H, s), 1.25 (9H, s), 1.43 (3H, s), 1.90 (3H, s), 2.12 (3H, s), 2.24 (3H, s), 4.26 (1H, s), 6.60-7.40 (4H, m), 9.46 (2H, br s), 1H unidentified.

[0125]

10 Reference Example 80

3-(4-Isopropylphenyl)-2,2,4,5,7-pentamethyl-2,3-dihydro-1-benzofuran-6-amine

To a solution of 4-bromocumene (2.01 g, 10.1 mmol) in THF (20 mL) was added dropwise a solution of n-
15 butyllithium in hexane (1.60 M, 6.25 mL, 10.0 mmol) under argon atmosphere at -78°C, and the mixture was stirred at the same temperature for 30 minutes. Then, to the reaction solution was added dropwise a solution of 2,2,4,5,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-6-ylformamide
20 obtained in Reference Example 76 (500 mg, 2.02 mmol) in THF (5 mL) at the same temperature, and the reaction solution was stirred at room temperature for 1 hour, followed by addition of water, which was extracted with ethyl acetate. The organic layer was washed with water and saturated brine,
25 dried over anhydrous sodium sulfate and then concentrated

under reduced pressure. The residue was purified by silica gel column chromatography (silica gel 30 g, hexane : ethyl acetate = 4 : 1) to obtain 3-hydroxy-3-(4-isopropylphenyl)-2,2,4,5,7-pentamethyl-2,3-dihydro-1-benzofuran-6-

5 ylformamide. To a mixture of said compound with trifluoroacetic acid (5 mL) was added triethylsilane (0.5 mL, 3.2 mmol) with ice-cooling, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and to the residue was
10 added a saturated sodium hydrogen carbonate solution to alkalify the aqueous layer, which was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure.

15 To a solution of the obtained residue in methanol (20 mL) was added concentrated hydrochloric acid, and the mixture was heated under reflux for 2 hours. The solvent was distilled off under reduced pressure and the residue was neutralized with a 12 N aqueous sodium hydroxide
20 solution. After extracting with ethyl acetate, the organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate =
25 4 : 1) to obtain 440 mg (yield 67%) of the title compound.

Melting point: 120 - 121°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.21 (6H, d, J = 7.0 Hz),
1.48 (3H, s), 1.84 (3H, s), 2.01 (3H, s), 2.10 (3H, s),
2.85 (1H, septet, J = 6.9 Hz), 3.58 (2H, br s), 4.07 (1H,
5 s), 6.60-7.12 (4H, m).

[0126]

Reference Example 81

3-(4-Isopropylphenyl)-2,2,4,6-tetramethyl-2,3-dihydro-1-
benzofuran-5-amine

10 Using tert-butyl (2,2,4,6-tetramethyl-3-oxo-2,3-
dihydro-1-benzofuran-5-yl)carbamate obtained in Reference
Example 60 and 4-bromocumene, the title compound was
synthesized in the same manner as in Reference Example 80.
Yield 89%. Melting point: 98 - 100°C (methanol).

15 ¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.21 (6H, d, J = 7.2 Hz),
1.48 (3H, s), 1.79 (3H, s), 2.18 (3H, s), 2.85 (1H, septet,
J = 7.2 Hz), 4.06 (1H, s), 4.60 (2H, br s), 6.49 (1H, s),
6.60-7.10 (4H, m).

[0127]

20 Reference Example 82

3-Benzyl-2,2,4,5,7-pentamethyl-2,3-dihydro-1-benzofuran-6-
amine

A solution of (2,2,4,5,7-pentamethyl-3-oxo-2,3-
dihydro-1-benzofuran-6-yl)formamide obtained in Reference
25 Example 76 (600 mg, 2.43 mmol) in THF (5 mL) was added

dropwise to a solution of benzylmagnesium chloride (a 1.6 M hexane solution, 6.25 mL, 10.0 mmol) in THF (20 mL) and n-butyl lithium (1.60 M, 6.25 mL, 10.0 mmol) in hexane at 0°C under argon atmosphere, and the mixture was stirred at room temperature for 2 hours. Water was added thereto, which was extracted with ethyl acetate. The organic layer was washed with 1 N hydrochloric acid, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain (3-benzyl-3-hydroxy-2,2,4,5,7-pentamethyl-2,3-dihydro-1-benzofuran-6-yl)formamide. To a mixture of said compound with trifluoroacetic acid (5 mL) was added triethylsilane (0.5 mL, 3.2 mmol) with ice-cooling, and the mixture was stirred at room temperature for 30 minutes. The reaction solution was concentrated under reduced pressure, and to the residue was added a saturated sodium hydrogen carbonate solution to alkalify the aqueous layer, which was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. To a solution of the obtained residue in methanol (20 mL) was added concentrated hydrochloric acid (10 ml), and the mixture was heated under reflux for 2 hours. The solvent was distilled off under reduced pressure and the residue

was neutralized with a 12 N aqueous sodium hydroxide solution. After extracting with ethyl acetate, the organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 440 mg (yield 62%) of the title compound. Melting point: 75 - 76°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.26 (3H, s), 1.40 (3H, s), 1.79 (3H, s), 1.98 (3H, s), 2.05 (3H, s), 2.74 (1H, dd, J = 14.4, 5.7 Hz), 2.88 (1H, dd, J = 14.4, 8.4 Hz), 3.25 (1H, dd, J = 14.4, 8.4 Hz), 3.53 (2H, br s), 7.10-7.28 (5H, m).

[0128]

Reference Example 83

5-Amino-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-3-ol

To a solution of 4-bromotoluene (2.73 g, 16.0 mmol) in THF (30 mL) was added dropwise a solution of n-butyllithium in hexane (1.60 M, 10.0 mL, 16.0 mmol) under argon atmosphere at -78°C, and the mixture was stirred at the same temperature for 30 minutes. Then, to the reaction solution was added dropwise a solution of 5-amino-2,2,4,6,7-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 57 (1.0 g, 4.56 mmol) in THF (10 mL) at the same temperature, and the reaction solution was stirred

at room temperature for 1 hour, followed by addition of water, which was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1), to obtain 921 mg (yield 65%) of the title compound. Melting point: 165 - 166°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.85 (3H, s), 1.50 (3H, s), 1.83 (3H, s), 2.11 (1H, s), 2.14 (3H, s), 2.18 (3H, s), 2.34 (3H, s), 3.31 (2H, br s), 6.80-7.70 (4H, m).

[0129]

Reference Example 84

5-Amino-2,2,4,6,7-pentamethyl-3-(2-naphthyl)-2,3-dihydro-1-benzofuran-3-ol

Using 5-amino-2,2,4,6,7-pentamethyl-1-benzofuran-3(2H)-one obtained in Reference Example 57 and 2-bromonaphthalene, the title compound was synthesized in the same manner as in Reference Example 83. Yield 66%. Melting point: 121 - 122°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.88 (3H, s), 1.56 (3H, s), 1.79 (3H, s), 2.16 (3H, s), 2.22 (3H, s), 2.42 (1H, s), 3.32 (2H, br s), 7.07 - 7.21 (1H, m), 7.37-8.00 (5H, m), 8.16-8.31 (1H, m).

[0130]

Reference Example 85

1-(4-Isopropylphenyl)-1-(2-methoxyphenyl)-2-methylpropan-1-ol

To a solution of 2-bromoanisole (5.0 g, 26.7 mmol) in THF (50 mL) was added n-butyllithium (1.6 M, 18 mL, 29 mmol) at -78°C, and the mixture was stirred at the same temperature for 30 minutes. To the reaction solution was added 1-(4-isopropylphenyl)-2-methylpropan-1-one (5.70 g, 30.0 mmol), and the mixture was stirred at room temperature for 1 hour. Water was poured into the reaction mixture which was extracted with ethyl acetate, and the combined organic layer was washed with water, dried over magnesium sulfate, filtered and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 20 : 1) to obtain 3.4 g (yield 43%) of the title compound. Melting point: 85 - 86°C (methanol).

¹H-NMR (CDCl₃) δ: 0.76 (3H, d, J = 6.9 Hz), 0.94 (3H, d, J = 6.9 Hz), 1.20 (6H, d, J = 6.9 Hz), 2.68 (1H, septet, J = 6.9 Hz), 2.83 (1H, septet, J = 6.9 Hz), 3.59 (3H, s), 4.91 (1H, s), 6.82 (1H, d, J = 8.1 Hz), 6.99 (1H, dt, J = 7.5, 1.5 Hz), 7.06 (2H, d, J = 7.5 Hz), 7.13-7.25 (3H, m), 7.52 (1H, dd, J = 7.5, 1.5 Hz).

[0131]

Reference Example 86

3-(4-Isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-benzofuran

A mixture of 1-(4-isopropylphenyl)-1-(2-methoxyphenyl)-2-methylpropan-1-ol obtained in Reference Example 85 (3.4 g, 11.4 mmol), 48% hydrobromic acid (50 mL) and acetic acid (10 mL) was heated under reflux under argon atmosphere for 16 hours. After cooling, water was added to the reaction solution, which was extracted with ethyl acetate, and the combined organic layer was washed with water, dried over magnesium sulfate, filtered and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (silica gel 50 g, hexane : ethyl acetate = 20 : 1) to obtain 2.71 g (yield 89%) of the title compound. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (3H, s), 1.24 (6H, d, $J = 7.2$ Hz), 1.59 (3H, s), 2.89 (1H, septet, $J = 7.2$ Hz), 4.33 (1H, s), 6.77-6.89 (2H, m), 6.98-7.06 (3H, m), 7.12-7.19 (3H, m).

[0132]

Reference Example 87

5-Bromo-3-(4-isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-benzofuran

Using 3-(4-isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-benzofuran obtained in Reference Example 86, the title compound was synthesized in the same manner as in Reference Example 23. Yield: quantitative. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (3H, s), 1.25 (6H, d, $J = 6.9$ Hz), 1.57 (3H, s), 2.89 (1H, septet, $J = 6.9$ Hz), 4.30 (1H, s),

6.69 (1H, d, $J = 8.2$ Hz), 6.99 (2H, d, $J = 8.1$ Hz), 7.12-7.28 (4H, m).

[0133]

Reference Example 88

5 N-Benzyl-3-(4-isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-amine

Using 5-bromo-3-(4-isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-benzofuran obtained in Reference Example 83, the title compound was synthesized in the same manner as in
10 Reference Example 24. Yield 46%. Melting point: 85 - 86°C (methanol).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.93 (3H, s), 1.25 (6H, d, $J = 7.0$ Hz), 1.57 (3H, s), 2.89 (1H, septet, $J = 7.0$ Hz), 3.62 (1H, br s), 4.22 (2H, s), 4.26 (1H, s), 6.40-6.55 (2H, m), 6.68 (1H, d,
15 $J = 8.2$ Hz), 7.02 (2H, d, $J = 8.0$ Hz), 7.15 (2H, d, $J = 8.0$ Hz), 7.20-7.40 (5H, m).

[0134]

Reference Example 89

3-(4-Isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-
20 benzofuran-5-amine

Using N-benzyl-3-(4-isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 88, the title compound was synthesized in the same manner as in Reference Example 30. Yield 98%. Melting point: 109
25 - 110°C (hexane).

¹H-NMR (CDCl₃) δ: 0.94 (3H, s), 1.24 (6H, d, J = 6.9 Hz), 1.55 (3H, s), 2.89 (1H, septet, J = 6.9 Hz), 3.33 (2H, br s), 4.23 (1H, s), 6.44 (1H, d, J = 2.1 Hz), 6.52 (1H, d, J = 8.1, 2.1 Hz), 6.63 (1H, d, J = 8.2 Hz), 7.02 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 8.1 Hz).

[0135]

Reference Example 90

1-Isopropyl-4-(2-methyl-3-(4-methylphenoxy)propene-1-yl) benzene

10 To a solution of p-cresol (3.50 g, 32.3 mmol) in DMF (70 mL) was added sodium hydride (a 60% liquid paraffin dispersion, 1.42 g, 35.5 mmol) under nitrogen atmosphere at 0°C, and the mixture was stirred at the same temperature for 30 minutes. To the reaction solution was added 1-(3-
15 bromo-2-methyl-1-propenyl)-4-isopropyl benzene (9.0 g, 35.5 mmol), and the mixture was stirred at room temperature for 3 hours. Water was added to the reaction solution, and the product was extracted with diisopropyl ether. The extract was washed with water, dried over magnesium sulfate, and
20 then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (silica gel 50 g, hexane : ethyl acetate = 20 : 1) to obtain 8.20 g (yield 91%) of the title compound. Oily matter.

25 ¹H-NMR (CDCl₃) δ: 1.25 (6H, d, J = 6.6 Hz), 1.98 (3H, s),

2.21 (3H, s), 2.90 (1H, septet, $J = 7.0$ Hz), 4.53 (2H, s),
6.58 (1H, s), 6.86 (2H, d, $J = 8.8$ Hz), 7.08 (2H, d, $J =$
8.8 Hz), 7.14-7.25 (4H, m).

[0136]

5 Reference Example 91

4-((3-(4-Isopropylphenyl)-2-methyl-2-propenyl)oxy)-2,6-
dimethylphenyl acetate

Using 4-hydroxy-2,6-dimethylphenyl acetate, the title
compound was synthesized in the same manner as in Reference
10 Example 90. Yield 83%. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (6H, d, $J = 7.2$ Hz), 1.97 (3H, s),
2.12 (6H, s), 2.32 (3H, s), 2.90 (1H, septet, $J = 7.2$ Hz),
4.49 (2H, s), 6.57 (1H, s), 6.66 (2H, s), 7.18-7.25 (4H, m).

[0137]

15 Reference Example 92

2-(1-(4-Isopropylphenyl)-2-methyl-2-propenyl)-4-
methylphenol

A solution of 1-isopropyl-4-(2-methyl-3-(4-
methylphenoxy)propene-1-yl)benzene obtained in Reference
20 Example 90 (8.2 g, 29.2 mmol) in N,N -dimethylaniline (50mL)
was stirred under argon atmosphere at 215°C for 16 hours.
After cooling, the reaction mixture was diluted with
diisopropyl ether, washed with 5 N hydrochloric acid and
water, dried over magnesium sulfate, and then concentrated
25 under reduced pressure. The obtained residue was purified

by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 7.80 g (yield 95%) of the title compound. Oily matter.

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, J = 7.2 Hz), 1.83 (3H, s),
5 2.22 (3H, s), 2.89 (1H, septet, J = 7.2 Hz), 4.61 (1H, s),
4.75 (1H, s), 5.04 (1H, s), 5.12 (1H, s), 6.70-6.78 (2H, m),
6.94 (1H, d, J = 8.0 Hz), 7.09 (2H, d, J = 8.6 Hz), 7.17
(2H, d, J = 8.6 Hz).

[0138]

10 Reference Example 93

3-(4-Isopropylphenyl)-2,2,5-trimethyl-2,3-dihydro-1-benzofuran

Using 2-(1-(4-isopropylphenyl)-2-methyl-2-propenyl)-4-methylphenol obtained in Reference Example 92, the title
15 compound was synthesized in the same manner as in Reference Example 86. Yield 37%. Melting point: 65 - 66°C.

¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.25 (6H, d, J = 6.9 Hz),
1.57 (3H, s), 2.25 (3H, s), 2.89 (1H, septet, J = 6.9 Hz),
4.28 (1H, s), 6.71 (1H, d, J = 8.1 Hz), 6.86 (1H, s), 6.93-
20 7.03 (3H, m), 7.15 (2H, d, J = 7.8 Hz).

[0139]

Reference Example 94

3-(4-Isopropylphenyl)-5-methoxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran

25 A solution of 4-((3-(4-isopropylphenyl)-2-

methylpropene-2-yl)oxy)-2,6-dimethylphenyl acetate obtained in Reference Example 91 (6.3 g, 17.9 mmol) in N,N-dimethylaniline (30 mL) was stirred under argon atmosphere at 215°C for 16 hours. After cooling, the reaction mixture was diluted with diisopropyl ether, washed with 5 N hydrochloric acid and water, dried over magnesium sulfate, and then concentrated under reduced pressure. A mixture of the obtained residue and 48% hydrobromic acid (30 mL) - acetic acid (5 mL) was heated under reflux under argon atmosphere for 16 hours. After cooling, water was added to the reaction solution, which was extracted with ethyl acetate, and the combined organic layer was washed with water, dried over magnesium sulfate, filtered and then concentrated under reduced pressure. To a solution of the obtained residue in DMF (30 mL) was added sodium hydride (a 60% liquid paraffin dispersion, 556 mg, 13.9 mmol) under nitrogen atmosphere at 0°C, and the mixture was stirred at the same temperature for 30 minutes. To the reaction solution was added methyl iodide (1.97 g, 13.9 mmol), and the mixture was stirred at room temperature for 3 hours. To the reaction solution, is added water, and the product was extracted with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography

(hexane : ethyl acetate = 4 : 1) to obtain 2.10 g (yield 36%) of the title compound as an oily matter. Melting point: 121 - 123°C (methanol).

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.22 (6H, d, J = 7.2 Hz),
5 1.49 (3H, s), 1.85 (3H, s), 2.27 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.63 (3H, s), 4.06 (1H, s), 6.49 (1H, s), 6.51 - 7.11 (4H, m).

[0140]

Reference Example 95

10 7-Bromo-3-(4-isopropylphenyl)-2,2,5-trimethyl-2,3-dihydro-1-benzofuran

Using 3-(4-isopropylphenyl)-2,2,5-trimethyl-2,3-dihydro-1-benzofuran obtained in Reference Example 93, the title compound was synthesized in the same manner as in

15 Reference Example 18. Yield 86%. Oily matter.

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.25 (6H, d, J = 6.9 Hz),
1.61 (3H, s), 2.23 (3H, s), 2.89 (1H, septet, J = 6.9 Hz),
4.35 (1H, s), 6.77 (1H, s), 6.99 (2H, d, J = 8.1 Hz), 7.10-7.21 (3H, m).

20 [0141]

Reference Example 96

7-Bromo-3-(4-isopropylphenyl)-5-methoxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran

Using 3-(4-isopropylphenyl)-5-methoxy-2,2,4,6-

25 tetramethyl-2,3-dihydro-1-benzofuran obtained in Reference

Example 94, the title compound was synthesized in the same manner as in Reference Example 18. Yield: quantitative.

Oily matter.

¹H-NMR (CDCl₃) δ: 1.05 (3H, s), 1.23 (6H, d, J = 7.0 Hz),
5 1.53 (3H, s), 1.82 (3H, s), 2.36 (3H, s), 2.86 (1H, septet,
J = 7.0 Hz), 3.62 (3H, s), 4.08 (1H, s), 6.60-7.20 (4H, m).

[0142]

Reference Example 97

N-Benzyl-3-(4-isopropylphenyl)-2,2,5-trimethyl-2,3-dihydro-
10 1-benzofuran-7-amine

Using 7-bromo-3-(4-isopropylphenyl)-2,2,5-trimethyl-
2,3-dihydro-1-benzofuran obtained in Reference Example 95,
the title compound was synthesized in the same manner as in
Reference Example 24. Yield 79%. Melting point: 80 - 81°C
15 (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.94 (3H, s), 1.24 (6H, d, J = 6.9 Hz),
1.56 (3H, s), 2.20 (3H, s), 2.89 (1H, septet, J = 6.9 Hz),
4.01 (1H, br s), 4.28 (2H, s), 4.37 (1H, s), 6.27 (1H, s),
6.37 (1H, s), 7.02 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 8.1
20 Hz), 7.21 - 7.44 (5H, m).

[0143]

Reference Example 98

N-Benzyl-3-(4-isopropylphenyl)-5-methoxy-2,2,4,6-
tetramethyl-2,3-dihydro-1-benzofuran-7-amine

25 Using 7-bromo-3-(4-isopropylphenyl)-5-methoxy-2,2,4,6-

tetramethyl-2,3-dihydro-1-benzofuran obtained in Reference Example 96, the title compound was synthesized in the same manner as in Reference Example 24. Yield 79%. Oily matter.

¹H-NMR (CDCl₃) δ: 0.98 (3H, s), 1.22 (6H, d, J = 6.9 Hz),
5 1.44 (3H, s), 1.78 (3H, s), 2.14 (3H, s), 2.85 (1H, septet,
J = 6.9 Hz), 3.42-3.67 (4H, m), 4.01 (1H, s), 4.35 (1H, d,
J = 14.4 Hz), 4.42 (1H, d, J = 14.4 Hz), 6.50-7.18 (4H, m),
7.20-7.38 (5H, m).

[0144]

10 Reference Example 99

3-(4-Isopropylphenyl)-2,2,5-trimethyl-2,3-dihydro-1-
benzofuran-7-amine

Using N-benzyl-3-(4-isopropylphenyl)-2,2,5-trimethyl-
2,3-dihydro-1-benzofuran-7-amine obtained in Reference

15 Example 97, the title compound was synthesized in the same
manner as in Reference Example 30. Yield 65%. Oily matter.

¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.24 (6H, d, J = 7.2 Hz),
1.56 (3H, s), 2.18 (3H, s), 2.88 (1H, septet, J = 7.2 Hz),
3.50 (2H, br s), 4.26 (1H, s), 6.31 (1H, s), 6.43 (1H, s),
20 7.02 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 8.1 Hz).

[0145]

Reference Example 100

3-(4-Isopropylphenyl)-5-methoxy-2,2,4,6-tetramethyl-2,3-
dihydro-1-benzofuran-7-amine

25 Using N-benzyl-3-(4-isopropylphenyl)-5-methoxy-

2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-7-amine
obtained in Reference Example 98, the title compound was
synthesized in the same manner as in Reference Example 30.
Yield 83%. Melting point: 111 - 112°C (ethyl acetate -
5 hexane).

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.22 (6H, d, J = 6.9 Hz),
1.50 (3H, s), 1.78 (3H, s), 2.14 (3H, s), 2.86 (1H, septet,
J = 6.9 Hz), 3.44 (2H, br s), 3.60 (3H, s), 4.08 (1H, s),
6.62-7.11 (4H, m).

10 [0146]

Reference Example 101

N-Benzyl-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-
amine

To a solution of 5-(benzylamino)-2,2,4,6-tetramethyl-
15 1-benzofuran-3(2H)-one obtained in Reference Example 51
(8.5 g, 28.8 mmol) in methanol (20 mL) was added sodium
borohydride (2.18 g, 57.6 mmol) at room temperature, and
the mixture was stirred for 2 hours. The reaction solution
was concentrated under reduced pressure, and the residue
20 was extracted with ethyl acetate. The organic layer was
washed with water, dried over anhydrous sodium sulfate, and
concentrated under reduced pressure to obtain the crude
product, 5-(benzylamino)-2,2,4,6-tetramethyl-2,3-dihydro-1-
benzofuran-3-ol. To a mixture of said compound with
25 trifluoroacetic acid (30 mL) was added triethylsilane (10

mL, 64 mmol) with ice-cooling, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and to the residue was added a saturated sodium hydrogen carbonate solution to
5 alkalify the aqueous layer, which was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The obtained residue was crystallized with ethyl acetate - hexane to
10 obtain 4.1 g (yield 51%) of the title compound. Melting point: 80 - 81°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.47 (6H, s), 2.18 (3H, s), 2.23 (3H, s), 2.83 (1H, br s), 2.91 (2H, s), 3.96 (2H, s), 6.43 (1H, s), 7.25-7.42 (5H, m).

15 [0147]

Reference Example 102

tert-Butyl (2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate

A mixture of N-benzyl-2,2,4,6-tetramethyl-2,3-dihydro-
20 1-benzofuran-5-amine obtained in Reference Example 101 (4.1 g, 14.6 mmol), 10% palladium carbon (50% hydrate, 400 mg), ammonium formate (1.84 g, 29.2 mmol) in methanol (70 mL) was heated under reflux for 2 hours. The catalyst was removed by filtration, and the filtrate was concentrated
25 under reduced pressure. To the residue was added water and

ethyl acetate, the organic layer was separated, and the water layer was extracted with ethyl acetate. The combined organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, and the resulting residue was crystallized from ethyl acetate - hexane to obtain 2.60 g (yield 72%) of 2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-ylamine. A solution of this compound (2.60 g, 13.5 mmol) and di-tert-butyl dicarbonate (6.20 mL, 27.0 mmol) in THF (50 mL) was heated under reflux for 16 hours. To the reaction solution was added water, the organic layer was separated, and the water layer was extracted with ethyl acetate. The combined organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, and the resulting residue was crystallized from hexane - ethyl acetate to obtain 2.57 g (yield 60%) of the title compound. Melting point: 121 - 123°C.

¹H-NMR (CDCl₃) δ: 1.45 (6H, s), 1.50 (9H, s), 2.11 (3H, s), 2.19 (3H, s), 2.90 (2H, s), 5.72 (1H, br s), 6.44 (1H, s), .

[0148]

Reference Example 103

tert-Butyl (7-bromo-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate

Using (2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-

yl)carbamic acid obtained in Reference Example 102, the title compound was synthesized in the same manner as in Reference Example 18. Yield 54%. Melting point: 115 - 117°C.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.38-1.59 (15H, m), 2.08 (3H, s), 2.31 (3H, s), 3.01 (2H, s), 5.81 (1H, br s).

[0149]

Reference Example 104

3-(4-Isopropylphenyl)-2-methyl-2-ethyl acrylate

10 To a suspension of sodium hydride (a 60% liquid paraffin dispersion, 5.92 g, 148 mmol) in DMF (150 mL) was added triethyl 2-phosphonopropionate (35.0 g, 148 mmol) at 0°C, and the mixture was stirred at the same temperature for 10 minutes. To the reaction solution was added 4-
15 isopropylbenzaldehyde (20.0 g, 135 mmol), and the mixture was stirred at room temperature 30 minutes. Water was added to the reaction solution, and the product was extracted twice with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate, and
20 then concentrated under reduced pressure to obtain 30.1 g (yield 96%) of the oily title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (6H, d, $J = 7.0$ Hz), 1.35 (3H, t, $J = 7.0$ Hz), 2.13 (3H, s), 2.92 (1H, septet, $J = 7.0$ Hz), 4.27 (2H, q, $J = 7.0$ Hz), 7.21 - 7.38 (4H, m), 7.67 (1H, s).

25 [0150]

Reference Example 105

Ethyl 2-methyl-3-(4-methylphenyl)-2-acrylate

Using 4-methylbenzaldehyde, the title compound was synthesized in the same manner as in Reference Example 104.

5 Yield 91%. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.34 (3H, t, $J = 7.0$ Hz), 2.12 (3H, d, $J = 1.4$ Hz), 2.37 (3H, s), 4.26 (2H, q, $J = 7.0$ Hz), 7.19 (2H, d, $J = 8.4$ Hz), 7.31 (2H, d, $J = 8.4$ Hz), 7.66 (1H, s).

[0151]

10 Reference Example 106

Ethyl 3-(4-fluorophenyl)-2-methyl-2-acrylate

Using 4-fluorobenzaldehyde, the title compound was synthesized in the same manner as in Reference Example 104. Yield 97%. Oily matter.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.35 (3H, t, $J = 7.0$ Hz), 2.10 (3H, d, $J = 1.2$ Hz), 4.28 (2H, q, $J = 7.0$ Hz), 7.08 (2H, t, $J = 8.8$ Hz), 7.32-7.43 (2H, m), 7.65 (1H, s).

[0152]

Reference Example 107

20 Ethyl (E)-3-(4-isopropylphenyl)-2-acrylate

To a suspension of sodium hydride (a 60% liquid paraffin dispersion, 10.4 g, 260 mmol) in DMF (200 mL) was added triethyl phosphonoacetate (58.2 g, 236 mmol) at 0°C , and the mixture was stirred at the same temperature for 10
25 minutes. To the reaction solution was added 4-

isopropylbenzaldehyde (35.0 g, 260 mmol) and the mixture was stirred at room temperature for 30 minutes. Water was added to the reaction solution, and the product was twice extracted with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure to obtain the oily title compound 47.5 g (yield 92%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (6H, d, $J = 7.0$ Hz), 1.33 (3H, t, $J = 7.0$ Hz), 2.92 (1H, septet, $J = 7.0$ Hz), 4.26 (2H, q, $J = 7.0$ Hz), 6.40 (1H, d, $J = 15.8$ Hz), 7.24 (2H, d, $J = 8.2$ Hz), 7.46 (2H, d, $J = 8.2$ Hz), 7.67 (1H, d, $J = 15.8$ Hz).

[0153]

Reference Example 108

3-(4-Isopropylphenyl)-2-methyl-2-propen-1-ol

To a suspension of ethyl 3-(4-isopropylphenyl)-2-methyl-2-acrylate (9.00 g, 38.7 mmol) obtained in Reference Example 104 and cerous chloride (1.00 g, 4.06 mmol) in THF (50 mL) was added lithium aluminum hydride (1.47 g, 38.7 mmol) in four batches for 30 minutes, and the mixture was stirred at the same temperature for 30 minutes. Water was added to the reaction solution, and the product was twice extracted with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane :

ethyl acetate = 8 : 1) to obtain the oily title compound
6.30 g (yield 86%).

¹H-NMR (CDCl₃) δ: 1.25 (6H, d, J = 7.0 Hz), 1.91 (3H, d, J
= 1.4 Hz), 2.90 (1H, septet, J = 7.0 Hz), 4.17 (2H, d, J =
5 0.8 Hz), 6.49 (1H, dd, J = 2.6, 1.4 Hz), 7.15-7.25 (4H, m),
1H unidentified

[0154]

Reference Example 109

2-Methyl-3-(4-methylphenyl)-2-propen-1-ol

10 Using ethyl 2-methyl-3-(4-methylphenyl)-2-acrylate
synthesized in Reference Example 105, the title compound
was synthesized in the same manner as in Reference Example
108. Yield 42%. Oily matter.

¹H-NMR (CDCl₃) δ: 1.87 (3H, s), 2.32 (3H, s), 4.13 (2H, s),
15 6.46 (1H, s), 7.08-7.22 (4H, m), 1H unidentified

[0155]

Reference Example 110

3-(4-Fluorophenyl)-2-methyl-2-propen-1-ol

20 Using ethyl 3-(4-fluorophenyl)-2-methyl-2-acrylate
synthesized in Reference Example 106, the title compound
was synthesized in the same manner as in Reference Example
108. Yield 95%. Oily matter.

¹H-NMR (CDCl₃) δ: 1.98 (3H, d, J = 1.6 Hz), 4.11 (2H, s),
6.58 (1H, s), 7.01 (2H, t, J = 8.8 Hz), 7.18-7.28 (2H, m),
25 1H unidentified

[0156]

Reference Example 111

3-(4-Bromophenyl)-2-methyl-2-propen-1-ol

To a solution of sodium tert-butoxide (10.6 g, 110
5 mmol) in DMF (60 mL) was added triethyl phosphonoacetate
(26.2 g, 110 mmol) under argon atmosphere at -10°C and the
mixture was stirred at the same temperature for 1 hour. 4-
bromobenzaldehyde (18.5 g, 100 mmol) was added to the
solution at 10°C or lower, and the mixture was warmed to
10 room temperature, and then stirred for 2 hours. Water was
added to the reaction solution after ice-cooling, which was
extracted with toluene. The extract was washed with a
saturated brine, dried over sodium sulfate, and then
concentrated under reduced pressure. The obtained oily
15 matter was dissolved in toluene (200 mL), dihydrobis(2-
methoxyethoxy) sodium aluminate (a 70% toluene solution,
41.5 g, 144 mmol) was added dropwise at -10°C, and then the
mixture was stirred at the same temperature for 1 hour. A
10% aqueous potassium sodium tartrate solution was added to
20 separate the organic layer. The organic layer was washed
with a 10% aqueous potassium sodium tartrate solution and a
saturated brine, dried over sodium sulfate, and then
concentrated under reduced pressure. The obtained residue
was purified by silica gel column chromatography (hexane :
25 ethyl acetate = 2 : 1) to obtain 20.1 g (yield 88%) of the

title compound as an oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.54 (1H, t, $J = 6.0$ Hz), 1.87 (3H, d, $J = 1.2$ Hz), 4.19 (2H, d, $J = 6.0$ Hz), 6.46 (1H, s), 7.14 (2H, d, $J = 8.4$ Hz), 7.45 (2H, d, $J = 8.4$ Hz).

5 [0157]

Reference Example 112

(E)-3-(4-Isopropylphenyl)-2-propen-1-ol

Using ethyl (E)-3-(4-isopropylphenyl)-2-acrylate synthesized in Reference Example 107, the title compound
10 was synthesized in the same manner as in Reference Example 108. Yield 65%. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, d, $J = 7.0$ Hz), 2.79-3.00 (2H, m), 4.30 (2H, d, $J = 5.6$ Hz), 6.35 (1H, dt, $J = 15.8, 5.6$ Hz), 6.59 (1H, d, $J = 15.8$ Hz), 7.10-7.39 (4H, m).

15 [0158]

Reference Example 113

1-(3-Bromo-2-methyl-1-propenyl)-4-isopropylbenzene

To a solution of 3-(4-isopropylphenyl)-2-methyl-2-propen-1-ol synthesized in Reference Example 108 (6.30 g, 33.1 mmol) in isopropyl ether (50 mL) was added phosphorus tribromide (5.98 g, 22.1 mmol) with ice-cooling and the
20 mixture was stirred at room temperature for 30 minutes. Water was added to the reaction solution and the mixture was extracted with isopropyl ether. The organic layer was
25 washed with water and a saturated sodium hydrogen carbonate

solution, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to obtain the oily title compound 7.63 g (yield 91%)

¹H-NMR (CDCl₃) δ: 1.25 (6H, d, J = 7.0 Hz), 2.03 (3H, d, J = 1.4 Hz), 2.90 (1H, septet, J = 7.0 Hz), 4.15 (2H, d, J = 0.8 Hz), 6.62 (1H, s), 7.14-7.26 (4H, m).

[0159]

Reference Example 114

1-(3-Bromo-2-methyl-1-propenyl)benzene

10 Using 2-methyl-3-phenyl-2-propen-1-ol, the title compound was synthesized in the same manner as in Reference Example 113. Yield 89%. Oily matter.

¹H-NMR (CDCl₃) δ: 2.01 (3H, d, J = 1.4 Hz), 4.13 (2H, d, J = 0.8 Hz), 6.64 (1H, s), 7.19-7.44 (5H, m).

15 [0160]

Reference Example 115

1-(3-Bromo-2-methyl-1-propenyl)-4-methylbenzene

20 Using 2-methyl-3-(4-methylphenyl)-2-propen-1-ol synthesized in Reference Example 109, the title compound was synthesized in the same manner as in Reference Example 113. Yield 80%. Oily matter.

¹H-NMR (CDCl₃) δ: 2.01 (3H, s), 2.34 (3H, s), 4.13 (2H, s), 6.60 (1H, s), 7.09-7.22 (4H, m).

[0161]

25 Reference Example 116

1-(3-Bromo-2-methyl-1-propenyl)-4-fluorobenzene

Using 3-(4-fluorophenyl)-2-methyl-2-propen-1-ol synthesized in Reference Example 110, the title compound was synthesized in the same manner as in Reference Example 113. Yield 79%. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.87 (3H, s), 4.17 (2H, s), 6.48 (1H, s), 7.01 (2H, t, $J = 8.8$ Hz), 7.18-7.27 (2H, m).

[0162]

Reference Example 117

10 1-Bromo-4-(3-bromo-2-methyl-1-propenyl)benzene

To an acetonitrile solution (180 mL) of triphenylphosphine (24.3 g, 92.7 mmol) was added dropwise bromine (4.78 mL, 185 mmol) at 0°C and the mixture was stirred at the same temperature for 30 minutes. To the solution was added the acetonitrile solution (60 mL) of 3-(4-bromophenyl)-2-methyl-2-propen-1-ol obtained in Reference Example 111 (20.1 g, 88.3 mmol) and the mixture was stirred at 0°C for 1 hour. The reaction solution was concentrated under reduced pressure, diethyl ether (200 mL) was added to the residue, and the insolubles were filtered off. The solution was washed with a saturated brine, dried over sodium sulfate, and then concentrated under reduced pressure to obtain 25.0 g (yield 98%) of the title compound as an oily matter.

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.99 (3H, d, $J = 1.4$ Hz), 4.12 (2H, s),

6.57 (1H, s), 7.15 (2H, d, $J = 8.4$ Hz), 7.45 (2H, d, $J = 8.4$ Hz).

[0163]

Reference Example 118

5 1-((E)-3-Bromo-1-propenyl)-4-isopropylbenzene

Using (E)-3-(4-isopropylphenyl)-2-propen-1-ol synthesized in Reference Example 112, the title compound was synthesized in the same manner as in Reference Example 113. Yield 72%. Oily matter.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, d, $J = 7.0$ Hz), 2.89 (1H, septet, $J = 7.0$ Hz), 4.16 (2H, dd, $J = 7.8, 0.8$ Hz), 6.35 (1H, dt, $J = 15.4, 7.8$ Hz), 6.63 (1H, d, $J = 15.4$ Hz), 7.14-7.35 (4H, m).

[0164]

15 Reference Example 119

N-(4-((3-(4-Isopropylphenyl)-2-methyl-2-propenyl)oxy)-2,3,6-trimethylphenyl)formamide

To a solution of N-(4-hydroxy-2,3,6-trimethylphenyl)formamide (3.00 g, 16.7 mmol) in DMF (30mL)
20 was added sodium hydride (a 60% liquid paraffin dispersion, 0.74 g, 18.4 mmol) under nitrogen atmosphere at 0°C , and the mixture was stirred at the same temperature for 10 minutes. To the reaction solution was added 1-(3-bromo-2-methyl-1-propenyl)-4-isopropylbenzene synthesized in
25 Reference Example 113 (4.66 g, 18.4 mmol) and the mixture

was stirred at room temperature for 30 minutes. Water was added to the reaction solution and the product was twice extracted with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The obtained residue was crystallized from ethyl acetate - hexane to obtain 3.70 g (yield 63%) of the title compound. Melting point: 153 - 155°C.

¹H-NMR (CDCl₃) δ: 1.26 (6H, d, J = 7.0 Hz), 2.00 (3H, s), 2.07-2.34 (9H, m), 2.91 (1H, septet, J = 7.0 Hz), 4.54 (2H, d, J = 5.4 Hz), 6.59-6.84 (3H, m), 7.17-7.36 (4H, m), 7.98 (0.5H, d, J = 12.0 Hz), 8.41 (0.5H, s).

[0165]

Reference Example 120

N-(2,3,6-Trimethyl-4-((2-methyl-3-phenyl-2-propenyl)oxy)phenyl)formamide

Using 1-(3-bromo-2-methyl-1-propenyl)benzene synthesized in Reference Example 114, the title compound was synthesized in the same manner as in Reference Example 119. Yield 41%. Melting point: 152 - 154°C. (ethyl acetate - hexane)

¹H-NMR (CDCl₃) δ: 1.98 (3H, d, J = 1.6 Hz), 2.10-2.32 (9H, m), 4.54 (2H, d, J = 5.2 Hz), 6.65 (1H, s), 6.67 (1H, s), 6.69-6.90 (1H, m), 7.11-7.41 (5H, m), 7.98 (0.5H, d, J = 12.0 Hz), 8.41 (0.5H, d, J = 1.4 Hz).

[0166]

Reference Example 121

N-(2,3,6-Trimethyl-4-((2-methyl-3-(4-methylphenyl)-2-propenyl)oxy)phenyl)formamide

5 Using 1-(3-bromo-2-methyl-1-propenyl)-4-methylbenzene synthesized in Reference Example 115, the title compound was synthesized in the same manner as in Reference Example 119. Yield 44%. Melting point: 167 - 169°C.

10 ¹H-NMR (CDCl₃) δ: 1.98 (3H, s), 2.07-2.38 (9H, m), 2.35 (3H, s), 4.53 (2H, d, J = 6.6 Hz), 6.61 (1H, s), 6.66 (1H, d, J = 2.4 Hz), 6.82-7.09 (1H, m), 7.11-7.31 (4H, m), 7.98 (0.5H, d, J = 12.2 Hz), 8.38 (0.5H, s).

[0167]

Reference Example 122

15 N-(4-((3-(4-Fluorophenyl)-2-methyl-2-propenyl)oxy)-2,3,6-trimethylphenyl)formamide

 Using 1-(3-bromo-2-methyl-1-propenyl)-4-fluorobenzene synthesized in Reference Example 116, the title compound was synthesized in the same manner as in Reference Example 20 119. Yield 52%. Melting point: 164 - 165°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.96 (3H, s), 2.12-2.32 (9H, m), 4.53 (2H, d, J = 5.2 Hz), 6.60 (1H, s), 6.66 (1H, s), 6.71-6.95 (1H, m), 7.04 (2H, t, J = 8.8 Hz), 7.22-7.33 (2H, m), 8.04 (0.5H, 25 d, J = 12.0 Hz), 8.40 (0.5H, d, J = 1.4 Hz).

[0168]

Reference Example 123

N-(4-((3-(4-Bromophenyl)-2-methyl-2-propenyl)oxy)-2,3,6-trimethylphenyl)formamide

5 Using 1-bromo-4-(3-bromo-2-methyl-1-propenyl)benzene synthesized in Reference Example 117, the title compound was synthesized in the same manner as in Reference Example 119. Yield 79%.

¹H-NMR (CDCl₃) δ: 1.95-1.97 (3H, m), 2.18-2.27 (9H, m),
10 4.52 (2H, br d, J = 4.4 Hz), 6.58 (1H, br s), 6.65 (1H, br s), 6.78 (1H, br d, J = 15.0Hz), 7.17 (2H, d, J = 8.2 Hz), 7.47 (2H, d J = 8.2 Hz), 7.99 (0.5H, d, J = 8.1 Hz), 8.42 (0.5H, d, J = 1.5 Hz).

[0169]

15 Reference Example 124

N-(4-(((E)-3-(4-Isopropylphenyl)-2-propenyl)oxy)-2,3,6-trimethylphenyl)formamide

 Using 1-((E)-3-bromo-1-propenyl)-4-isopropylbenzene synthesized in Reference Example 118, the title compound
20 was synthesized. Yield 59%. Melting point: 165 - 167°C. (ethyl acetate - hexane)

¹H-NMR (CDCl₃) δ: 1.25 (6H, d, J = 6.8 Hz), 2.13-2.27 (9H, m), 2.90 (1H, septet, J = 6.8 Hz), 4.66 (2H, t, J = 5.8 Hz), 6.37 (1H, dt, J = 15.8, 5.8 Hz), 6.65-6.88 (3H, m), 7.16-
25 7.26 (2H, m), 7.35 (2H, d, J = 8.0 Hz), 7.98 (0.5H, d, J =

12.0 Hz), 8.40 (0.5H, d, $J = 1.4$ Hz).

[0170]

Reference Example 125

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-
5 benzofuran-5-amine

A solution of N-(4-((3-(4-isopropylphenyl)-2-methyl-2-propenyl)oxy)-2,3,6-trimethylphenyl)formamide synthesized in Reference Example 119 (3.70 g, 10.5 mmol) in N,N-dimethylaniline (20 mL) was stirred under argon atmosphere
10 at 215°C for 6 hours. After cooling, the reaction mixture was extracted with ethyl acetate, washed with 2 N hydrochloric acid and water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain the crude product of N-(4-hydroxy-3-(1-(4-isopropylphenyl)-2-methyl-2-propenyl)-2,5,6-trimethylphenyl)formamide. A
15 mixture of this compound (2.98 g, 8.47 mmol) and concentrated hydrochloric acid (20 mL) - methanol (60 mL) was heated under reflux under nitrogen atmosphere for 2 hours. The solvent was concentrated under reduced pressure,
20 and the obtained residue was neutralized with a 8 N aqueous sodium hydroxide solution. The product was twice extracted with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The obtained residue was
25 crystallized from isopropyl ether - hexane to obtain 2.23 g

(yield 66%) of the title compound. Melting point: 130 - 132°C.

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.21 (6H, d, J = 6.6 Hz), 1.47 (3H, s), 1.78 (3H, s), 2.12 (3H, s), 2.19 (3H, s),
5 2.40-2.60 (3H, m), 4.08 (1H, s), 6.72-7.00 (2H, m), 7.07 (2H, d, J = 8.0 Hz).

[0171]

Reference Example 126

2,2,4,6,7-Pentamethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-
10 amine

Using N-(2,3,6-trimethyl-4-((2-methyl-3-phenyl-2-propenyl)oxy)phenyl)formamide synthesized in Reference Example 120, the title compound was synthesized in the same manner as in Reference Example 125. Yield 67%. Melting
15 point: 129 - 131°C.

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.48 (3H, s), 1.77 (3H, s), 2.13 (3H, s), 2.19 (3H, s), 3.20 (2H, br s), 4.12 (1H, s), 6.70-7.30 (5H, m).

[0172]

20 Reference Example 127

2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine

Using N-(2,3,6-trimethyl-4-((2-methyl-3-(4-methylphenyl)-2-propenyl)oxy)phenyl)formamide synthesized
25 in Reference Example 121, the title compound was

synthesized in the same manner as in Reference Example 125.

Yield 57%. Melting point: 114 - 115°C (petroleum ether).

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.47 (3H, s), 1.77 (3H, s),
2.12 (3H, s), 2.19 (3H, s), 2.30 (3H, s), 3.23 (2H, br s),
5 4.08 (1H, s), 6.60-7.23 (4H, m).

[0173]

Reference Example 128

3-(4-Fluorophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-
benzofuran-5-amine

10 Using N-(4-((3-(4-fluorophenyl)-2-methyl-2-
propenyl)oxy)-2,3,6-trimethylphenyl)formamide synthesized
in Reference Example 122, the title compound was
synthesized in the same manner as in Reference Example 125.
Yield 78%. Melting point: 125 - 127°C (petroleum ether).
15 ¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.47 (3H, s), 1.77 (3H, s),
2.12 (3H, s), 2.19 (3H, s), 3.10 (2H, br s), 4.09 (1H, s),
6.62-7.20 (4H, m).

[0174]

Reference Example 129

20 3-(4-Bromophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-
benzofuran-5-amine

Using N-(4-((3-(4-bromophenyl)-2-methyl-2-
propenyl)oxy)-2,3,6-trimethylphenyl)formamide synthesized
in Reference Example 123, the title compound was
25 synthesized in the same manner as in Reference Example 125.

Yield 56%.

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.47 (3H, s), 1.77 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 3.23 (2H, br), 4.07 (1H, s), 6.83 (2H, br), 7.36 (2H, brd, J = 8.0 Hz).

5 [0175]

Reference Example 130

N-(4-Hydroxy-3-(1-(4-isopropylphenyl)-2-propenyl)-2,5,6-trimethylphenyl)formamide

10 A solution of N-(4-(((E)-3-(4-isopropylphenyl)-2-propenyl)oxy)-2,3,6-trimethylphenyl)formamide synthesized in Reference Example 124 (5.80 g, 17.2 mmol) in N,N-dimethylaniline (50 mL) was stirred under argon atmosphere at 215°C for 6 hours. After cooling, the reaction mixture was diluted with ethyl acetate, was washed with 2 N
15 hydrochloric acid and water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was crystallized from ethyl acetate to obtain 3.50 g (yield 60%) of the title compound. Melting point: 170 - 171°C.

20 ¹H-NMR (CDCl₃) δ: 1.18-1.40 (6H, m), 2.11-2.27 (9H, m), 2.77-3.00 (1H, m), 5.00-5.22 (2H, m), 5.30-5.42 (1H, m), 6.30-6.85 (2H, m), 7.10-7.37 (5H, m), 7.97 (0.5H, d, J = 12.2 Hz), 8.43 (0.5H, d, J = 1.4 Hz).

[0176]

Reference Example 131

25 3-(4-Isopropylphenyl)-2,4,6,7-tetramethyl-1-benzofuran-5-

amine hydrochloride

To a suspension of N-(4-hydroxy-3-(1-(4-isopropylphenyl)-2-propenyl)-2,5,6-trimethylphenyl)formamide synthesized in Reference Example 5 130 (3.50 g, 10.4 mmol) and calcium carbonate (1.35 g, 13.5 mmol) in THF (15 mL) - methanol (15 mL) was added slowly benzyltrimethylammonium iododichloride (3.90 g, 11.4 mmol). The reaction solution was stirred at room temperature for 30 minutes. After separating the insolubles, the solvent 10 was concentrated under reduced pressure, and ethyl acetate and water were added to the residue. The organic layer was separated and an aqueous layer was twice extracted with ethyl acetate. The combined organic layer was washed with a 10% sodium hydrosulfite aqueous solution, water, a 15 saturated sodium hydrogen carbonate solution and a saturated brine, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain 4.08 g of N-(2-iodomethyl-3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)formamide. A solution of this 20 compound (4.08 g, 8.81 mmol) and 1,8-diazabicyclo(5,4,0)-7-undecene (6.58 mL, 44.0 mmol) in toluene (30 mL) was stirred at 100°C under argon atmosphere for 3 hours. Water was added to the reaction solution, which was twice extracted with ethyl acetate. The extract was washed with 25 2 N hydrochloric acid and water, dried over magnesium

sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 20 : 1) to obtain N-(3-(4-isopropylphenyl)-2,4,6,7-tetramethyl-1-benzofuran-5-yl)formamide 2.40g. A mixture of this compound (2.40 g, 7.18 mmol) in hydrochloric acid (20 mL)-methanol (60 mL) was heated under reflux under nitrogen atmosphere for two hours. The solvent was concentrated under reduced pressure, and the obtained residue was neutralized with 8 N aqueous sodium hydroxide solution. The product was twice extracted with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to obtain the oily free base 1.80 g. The oily free base (0.50 g, 1.63 mmol) was dissolved in hydrochloric acid - methanol solution, the solvent was concentrated under reduced pressure, and the obtained residue was crystallized by methanol to obtain the object compound 0.41g (yield 41%). Melting point: 194 - 197°C. ¹H-NMR (CDCl₃) δ: 1.29 (6H, d, J = 7.0 Hz), 2.30 (6H, s), 2.41 (3H, s), 2.60 (3H, s), 2.94 (1H, septet, J = 7.0 Hz), 7.13-7.26 (4H, m), 10.1 (2H, br s), 1H unidentified

[0177]

Reference Example 132

4-Methoxy-2,3,6-trimethylaniline

N-(4-Hydroxy-2,3,6-trimethylphenyl)formamide (30.0 g,

167 mmol) was dissolved in a mixed solvent of 4 N potassium hydroxide aqueous solution (100mL) and methanol (300 mL), and dimethyl sulfate (42.0 g, 334 mmol) was added to the solution at room temperature and the mixture was heated under reflux for 14 hours. After ice-cooling, the precipitated crystals were collected by filtration to obtain the crude product of N-(4-methoxy-2,3,6-trimethylphenyl)formamide. To a suspension of the compound in methanol (200 mL) was added concentrated hydrochloric acid (50 mL) and the mixture was heated under reflux for 3 hours. The reaction mixture was cooled to room temperature, and then was neutralized with a 8 N aqueous sodium hydroxide solution. The product was twice extracted with ethyl acetate, and the combined extract was washed with 10% sodium hydrosulfite aqueous solution and water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was crystallized from isopropyl ether to obtain the object compound 21.0 g (yield 76%). Melting point: 70 - 72°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.11 (3H, s), 2.16 (3H, s), 2.18 (3H, s), 3.16 (1H, br s), 3.74 (3H, s), 6.54 (1H, s).

[0178]

Reference Example 133

tert-Butyl 4-methoxy-2,3,6-trimethylphenylcarbamate

To a solution of 4-methoxy-2,3,6-trimethylaniline

synthesized in Reference Example 132 (21.0 g, 127 mmol) and triethylamine (21.0 mL, 152 mmol) in THF (150 mL) was added di-tert-butyl dicarbonate (32 mL, 140 mmol) at room temperature, and the mixture was heated under reflux for 14 hours. The solvent was concentrated under reduced pressure. Water was poured into the residue, which was twice extracted with ethyl acetate. The combined organic layer was washed with 1 N hydrochloric acid and a saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered and then concentrated under reduced pressure. The residue was crystallized from ethyl acetate - hexane to obtain 25.2 g (yield 75%) of the title compound. Melting point: 104 - 106°C.

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 2.12 (3H, s), 2.17 (3H, s), 2.24 (3H, s), 3.78 (3H, s), 5.81 (1H, br s), 6.58 (1H, s).

[0179]

Reference Example 134

tert-Butyl 3-bromo-4-methoxy-2,5,6-trimethylphenylcarbamate

To a solution of tert-butyl 4-methoxy-2,3,6-trimethylphenylcarbamate synthesized in Reference Example 133 (12.7 g, 47.9 mmol) and sodium acetate (4.72 g, 57.5 mmol) in acetic acid (50 mL) was added bromine (8.42 g, 52.7 mmol) at room temperature and the mixture was stirred at the same temperature for 1 hour. Water (80 mL) was poured into the reaction mixture, and the precipitated

crystals were collected by filtration and then dissolved in ethyl acetate. The solution was washed with a saturated sodium hydrogen carbonate solution and water, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was crystallized from methanol to obtain 15.0 g (yield 91%) of the title compound. Melting point: 159 - 161°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (9H, s), 2.15 (3H, s), 2.24 (3H, s), 2.35 (3H, s), 3.74 (3H, s), 5.92 (1H, br s).

10 [0180]

Reference Example 135

2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine

To a solution of tert-butyl 3-bromo-4-methoxy-2,5,6-trimethylphenylcarbamate synthesized in Reference Example 134 (27.8 g, 80.8 mmol) in THF (150 mL) was added n-butyllithium (1.6 M, 110 mL, 176 mmol) hexane solution at -78°C and the mixture was stirred at the same temperature for 20 minutes. 2-Methyl-1-(4-methylphenyl)propane-1-one (13.1 g, 80.7 mmol) was added to the reaction solution, and the mixture was stirred at room temperature for 1 hour. Water (150 mL) was poured into the reaction mixture, which was three times extracted with ethyl acetate, the combined organic layer was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure to

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obtain the crude product 26.0 g of tert-butyl 3-(1-hydroxy-2-methyl-1-(4-methylphenyl)propyl)-4-methoxy-2,5,6-trimethylphenylcarbamate. A mixture of this compound and 47% hydrobromic acid (100 mL) was heated under reflux under argon atmosphere for 4 hours. The reaction mixture was cooled to room temperature, and then was neutralized with a 8 N aqueous sodium hydroxide solution. The product was twice extracted with ethyl acetate, and the combined extract was washed with a saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was crystallized from isopropyl ether - hexane to obtain 14.8 g (yield 62%) of the title compound. Melting point: 114 - 115°C.

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.47 (3H, s), 1.78 (3H, s), 2.12 (3H, s), 2.17 (3H, s), 2.30 (3H, s), 2.80 (2H, br s), 4.08 (1H, s), 6.60-7.10 (4H, m).

[0181]

Reference Example 136

(+)-2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine

2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine synthesized in Reference Example 135 was subjected to high performance liquid chromatography (apparatus: Waters Semi-Preparative System,

Column:CHIRALCEL OD (20 (i, d) × 250 mm) manufactured by Daicel Chemical Industries, Ltd., Mobile phase: hexane : isopropanol = 95 : 5, Flow rate: 5 mL/min, Column temperature: 30°C, Injection amount: 40 mg), to

5 preparatively separate a fraction with a shorter retention time. Melting point: 87 - 89°C. $[\alpha]_D^{20} = +4.7^\circ$ (c = 0.495, methanol).

[0182]

Reference Example 137

10 (-)-2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine

2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine synthesized in Reference Example 135 was subjected to high performance liquid chromatography

15 (apparatus: Waters Semi-Preparative System, Column:

CHIRALCEL OD (20 (i, d) × 250 mm) manufactured by Daicel Chemical Industries, Ltd., Moving phase: hexane :

isopropanol = 95 : 5, Flow rate: 5 mL/min, Column

temperature: 30°C, Injection amount: 40 mg), to

20 preparatively separate a fraction with a longer retention time. Melting point: 88 - 90°C. $[\alpha]_D^{20} = -4.3^\circ$ (c = 0.499, methanol).

[0183]

Reference Example 138

25 (+)-3-(4-Bromophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-

benzofuran-5-amine

Di-p-toluoyl-D-tartaric acid (3.86 g, 10 mmol) was dissolved in isopropanol (14.2 mL) at 70°C, and a solution of 3-(4-bromophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine synthesized in Reference Example 129 (3.60 g, 10 mmol) in acetonitrile (47.5 mL) was added dropwise thereto with maintaining the inside temperature of 60°C. The solution was cooled to 30°C for 3 hours, and then was stirred at the same temperature for 2 hours. The precipitated crystals were taken, and then were washed with a small amount of cold acetonitrile. The obtained, crude diastereomeric salt was suspended in acetonitrile (29.6 mL) and was stirred over night. The crystals were collected by filtration, washed with a small amount of cold acetonitrile, and then dried under reduced pressure. The crystals were suspended in ethyl acetate (100 mL), a saturated sodium hydrogen carbonate solution (100 mL) was added thereto, and the mixture was stirred thoroughly to separate the organic layer. The organic layer was washed with water (100 mL) and a saturated brine, and then was dried over anhydrous sodium sulfate. The solvent was dried under reduced pressure, and was crystallized with cold hexane to obtain 1.13 g (yield 31%) of the title compound. Melting point: 143 - 144°C (hexane). $[\alpha]_D^{20} = +11.6^\circ$ (c = 0.5, methanol). $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.00 (3H, s), 1.47 (3H, s), 1.77 (3H, s),

2.12 (3H, s), 2.18 (3H, s), 3.25 (2H, br s), 4.07 (1H, s),
6.85 (2H, br), 7.36 (2H, br d, J=6.9 Hz).

[0184]

Reference Example 139

5 (3R)-(+) -2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-
dihydro-1-benzofuran-5-amine

Using 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-
dihydro-1-benzofuran-5-amine synthesized in Reference
Example 127, the title compound was obtained in the same
10 manner as in Reference Example 138. Yield 39%. Melting
point: 87 - 89°C (hexane). $[\alpha]_D^{20} = +4.7^\circ$ (c = 0.5,
methanol).

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.00 (3H, s), 1.47 (3H, s), 1.78 (3H, s),
2.12 (3H, s), 2.18 (3H, s), 2.30 (3H, s), 2.78 (2H, br),
15 4.09 (1H, s), 6.83 (2H, br), 7.04 (2H, br d, J = 7.4 Hz).

[0185]

Reference Example 140

2-(2,3-Dimethylphenoxy)-2-methyl-1-(4-methylphenyl)propane-
1-ol

20 To a mixture of 2,3-dimethylphenol (12.2 g, 100 mmol)
and potassium carbonate (27.4 g, 200 mmol) in
dimethylsulfoxide (138 mL) was added 2-bromo-1-(4-
bromophenyl)-2-methylpropane-1-one (42.2 g, 175 mmol) at
room temperature, and the mixture was warmed to 35°C. The
25 mixture was stirred at the same temperature for 24 hours,

poured into cold water (300 mL), and then extracted with diethyl ether. The organic layer was washed with a 4 N aqueous sodium hydroxide solution and a saturated brine, and then was dried over sodium sulfate. The solvent was concentrated under reduced pressure, and then was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 9) to obtain 2-(2,3-dimethylphenoxy)-2-methyl-1-(4-methylphenyl)propane-1-one of oily matter. The obtained oily matter was dissolved in methanol (200 mL), sodium borohydride (3.8 g, 100 mmol) was added thereto at 0°C, and the mixture was warmed to room temperature. The oily matter was stirred at the same temperature for 1 hour, cooled to 0°C, and neutralized with 1 N hydrochloric acid, and then the solvent was distilled off under reduced pressure. The residue was extracted with ethyl acetate, and the extract solution was washed with a saturated brine, and then was dried over sodium sulfate. The solvent was distilled off under reduced pressure to obtain 17.1 g (yield 60%) of the title compound as an oily matter.

¹H-NMR (CDCl₃) δ: 1.12 (3H, s), 1.23 (3H, s), 2.19 (3H, s), 2.27 (3H, s), 2.35 (3H, s), 3.38 (1H, d, J = 2.0 Hz), 4.88 (1H, d, J = 2.0 Hz), 6.83-7.07 (3H, m), 7.14 (2H, d, J = 8.0 Hz), 7.37 (2H, d, J = 8.0 Hz).

[0186]

25 Reference Example 141

2,2,6,7-Tetramethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran

To a solution of 2-(2,3-dimethylphenoxy)-2-methyl-1-(4-methylphenyl)propane-1-ol synthesized in Reference
5 Example 140 (17.0 g, 60 mmol) in toluene (200 mL) was added trifluoromethanesulfonate (0.53 mL, 6 mmol) at 0°C, and the mixture was warmed to 50°C. The mixture was stirred at the same temperature for 30 minutes and was reacted under
10 reflux condition for 2 hours. The reaction solution was cooled to 0°C, and then was poured into a saturated sodium hydrogen carbonate solution. The organic layer was separated, washed with a saturated brine, and dried over sodium sulfate, and the solvent then was distilled off under reduced pressure. The residue was purified by silica
15 gel column chromatography (ethyl acetate : hexane = 1 : 9) to obtain 9.3 g (yield 58%) of the title compound as an oily matter.

¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.57 (3H, s), 2.16 (3H, s), 2.26 (3H, s), 2.33 (3H, s), 4.29 (1H, s), 6.66 (1H, d, J =
20 7.6 Hz), 6.74 (1H, d, J = 7.6, Hz), 6.98 (2H, d, J = 8.0 Hz), 7.19 (2H, d, J = 8.0 Hz).

[0187]

Reference Example 142

5-Bromo-2,2,6,7-tetramethyl-3-(4-methylphenyl)-2,3-dihydro-
25 1-benzofuran

Using 2,2,6,7-tetramethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran obtained in Reference Example 141, the title compound was synthesized in the same manner as in Reference Example 18. Yield 92%. Oily matter.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 0.95 (3H, s), 1.55 (3H, s), 2.22 (3H, s), 2.33 (3H, s), 2.34 (3H, s), 4.27 (1H, s), 6.96 (2H, d, $J = 8.0$ Hz), 7.04 (1H, s), 7.11 (2H, d, $J = 8.0$ Hz).

[0188]

Reference Example 143

10 N-Benzyl-2,2,6,7-tetramethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine

Using 5-bromo-2,2,6,7-tetramethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran obtained in Reference Example 142, the title compound was synthesized in the same manner as in
15 Reference Example 24. Yield 99%. Oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.92 (3H, s), 1.55 (3H, s), 2.09 (3H, s), 2.21 (3H, s), 2.33 (3H, s), 3.47 (2H, s), 4.17 (1H, s), 4.27 (1H, s), 6.31 (1H, s), 6.97 (2H, d, $J = 7.8$ Hz), 7.09 (2H, d, $J = 7.8$ Hz), 7.20-7.36 (5H, m).

20 [0189]

Reference Example 144

N-(2,2,6,7-Tetramethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran)-5-amine

To a solution of N-benzyl-2,2,6,7-tetramethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained in
25

Reference Example 143 (6.60 g, 17.8 mmol) in ethanol (70 mL) was added 12 N hydrochloric acid (0.1 mL) and 10% - palladium carbon (hydrous 50%, 0.33 g), and the mixture was stirred under hydrogen condition of 5 atmosphere pressure at room temperature for 2 hours. The catalyst is filtered off, and the solution was concentrated under reduced pressure. The residue was diluted with ethyl acetate, was washed with a saturated brine, and then was dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 4) to obtain 4.42 g (yield 88%) of the title compound as an oily matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.94 (3H, s), 1.54 (3H, s), 2.09 (3H, s), 2.18 (3H, s), 2.33 (3H, s), 3.25 (2H, br), 4.23 (1H, s), 6.30 (1H, s), 7.00 (2H, d, $J = 8.1$ Hz), 7.10 (2H, d, $J = 8.1$ Hz).

[0190]

Reference Example 145

N-(3-Hydroxy-2,2,6,7-tetramethyl-3-(3-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide (303 mg, 1 mmol) obtained in Reference Example 65 in THF (10 mL) was added dropwise at 0°C under an argon atmosphere a solution

of 3-tolylmagnesium bromide (1.0 M, 10 mL, 10 mmol) in THF which is commercially available, and the mixture was warmed to room temperature. The mixture was stirred for 1 hour, and the reaction solution was added to ice and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The obtained residue was recrystallized from ethyl acetate - hexane to obtain 265 mg (yield: 67%) of the title compound. Melting point: 113 - 114°C.

¹H-NMR (CDCl₃) δ: 0.86 (3H, s), 1.10 (9H, s), 1.59 (3H, s), 2.18-2.22 (8H, m), 2.36 (3H, s), 2.40 (1H, brs), 6.80 (1H, brs), 7.10-7.20 (2H, m), 7.22-7.26 (2H, m), 7.35 (1H, s).

[0191]

Reference Example 146

N-(3-Hydroxy-2,2,6,7-tetramethyl-3-(phenylethyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

A solution of 2-chloroethylbenzene (648 mg, 4.6 mmol) in THF (5 mL) was added dropwise under an argon atmosphere to a mixture of magnesium (112 mg, 4.6 mmol) and a catalytic amount of iodine, and the mixture was stirred for 30 minutes. To the reaction solution was added dropwise a solution of 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide (300 mg, 0.98 mmol) obtained in Reference Example 65 in THF (3 mL), and the

mixture was stirred at room temperature for 1 hour. The reaction solution was added to ice and the product was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate - hexane 5 : 95 - 40 : 60) and recrystallized from ethyl acetate - hexane to obtain 201 mg (yield: 51%) of the title compound. Melting point: 99 - 100°C.

¹H-NMR (CDCl₃) δ: 1.12 (9H, s), 1.37 (3H, s), 1.54 (3H, s), 1.99-2.30 (11H, m), 2.80 (1H, dt, J = 12.9, 4.8 Hz), 2.97 (1H, dt, J = 12.9, 4.8 Hz), 6.77 (1H, brs), 7.15-7.31 (6H, m).

[0192]

Reference Example 147

N-(3-Hydroxy-2,2,6,7-tetramethyl-3-(2-(trifluoromethoxy)phenyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of 1-bromo-2-(trifluoromethoxy)benzene (827 mg, 3.43 mmol) in THF (8 mL) was added dropwise at -78°C under an argon atmosphere n-butyllithium (1.59 M hexane solution, 1.85 mL, 2.94 mmol), and the mixture was stirred for 30 minutes. To the reaction solution was added dropwise at -78°C a solution of 3,3-dimethyl-N-(2,2,6,7-

tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide (300 mg, 0.98 mmol) obtained in Reference Example 65 in THF (3 mL), and the mixture was stirred for 30 minutes. The reaction solution was warmed to room temperature and stirred for 1 hour, and water was added to the reaction solution and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate - hexane 5 : 95 - 40 : 60), and then recrystallized from ethyl acetate - hexane to obtain 267 mg (yield: 59%) of the title compound. Melting point: 160 - 161°C.

¹H-NMR (CDCl₃) δ: 0.97 (3H, s), 1.11 (9H, s), 1.62 (3H, s), 2.18 (6H, s), 2.22 (2H, s), 3.00 (1H, brs), 6.79 (1H, brs), 7.15-7.36 (5H, m).

[0193]

Reference Example 148

N-(3-Hydroxy-2,2,6,7-tetramethyl-3-(2-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and commercially available 2-tolylmagnesium bromide, the title compound was synthesized in the same manner as in Reference Example 145. Yield: 43%. Melting

point: 111 - 112°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.10 (9H, s), 1.68 (3H, s), 2.17-2.26 (9H, m), 2.64 (3H, s), 6.82 (1H, brs), 6.90-7.26 (5H, m).

5 [0194]

Reference Example 149

N-(3-Hydroxy-2,2,6,7-tetramethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

10 Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and commercially available phenyllithium, the title compound was synthesized in the same manner as in Reference Example 146. Yield: 58%. Melting point: 109 - 111°C (ethyl acetate - hexane).

15 ¹H-NMR (CDCl₃) δ: 0.85 (3H, s), 1.10 (9H, s), 1.62 (3H, s), 2.18-2.22 (8H, m), 2.37 (1H, brs), 6.79 (1H, brs), 7.12 (1H, s), 7.27-7.38 (3H, m), 7.47-7.50 (2H, m).

[0195]

Reference Example 150

20 N-(3-Hydroxy-2,2,6,7-tetramethyl-3-(2-naphthyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

25 Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and 2-bromonaphthalene, the title compound was synthesized in the same manner as in Reference Example 146.

Yield: 65%. Melting point: 142 - 144°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.89 (3H, s), 1.09 (9H, s), 1.65 (3H, s), 2.20-2.24 (8H, m), 2.46 (1H, brs), 6.82 (1H, brs), 7.16 (1H, s), 7.46-7.51 (2H, m), 7.60 (1H, d, J = 8.8 Hz), 7.80-7.86 (3H, m), 7.99 (1H, s).

[0196]

Reference Example 151

N-(3-Hydroxy-3-(3-isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and 1-bromo-3-isopropylbenzene, the title compound was synthesized in the same manner as in Reference Example 146. Yield: 76%. Melting point: 136 - 137°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.84 (3H, s), 1.10 (9H, s), 1.22 (6H, d, J = 6.9 Hz), 1.60 (3H, s), 2.14-2.22 (9H, m), 2.90 (1H, septet, J = 6.9 Hz), 6.77 (1H, brs), 7.14-7.18 (2H, m), 7.23-7.28 (2H, m), 7.39 (1H, s).

[0197]

Reference Example 152

N-(3-Hydroxy-3-(2-methoxyphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-

dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and commercially available 2-methoxyphenylmagnesium bromide, the title compound was synthesized in the same manner as in Reference Example 145.

5 Yield: 58%. Melting point: 168 - 169°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.92 (3H, s), 1.10 (9H, s), 1.66 (3H, s), 2.15-2.21 (8H, m), 3.94 (3H, s), 5.17 (1H, brs), 6.82 (1H, brs), 6.89-6.97 (2H, m), 7.09 (1H, s), 7.12 (1H, d, J = 8.1 Hz), 7.28 (1H, d, J = 8.1 Hz).

[0198]

Reference Example 153

N-(3-Hydroxy-3-(4-isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

15 Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and 1-bromo-4-isopropylbenzene, the title compound was synthesized in the same manner as in Reference Example 146. Yield: 42%. Melting point: 119 - 121°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.84 (3H, s), 1.11 (9H, s), 1.26 (6H, d, J = 6.9 Hz), 1.60 (3H, s), 2.18-2.22 (8H, m), 2.29 (1H, s), 2.86 (1H, septet, J = 6.9 Hz), 6.80 (1H, br s), 7.15 (1H, s), 7.21 (2H, d, J = 8.0 Hz), 7.41 (2H, d, J = 8.0 Hz).

25 [0199]

Reference Example 154

N-(2,2,6,7-Tetramethyl-3-(2-thienyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and 2-bromothiophene, the title compound of oily matter was obtained in the same manner as in Reference Example 146. Yield: 86%.

¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.12 (9H, s), 1.64 (3H, s), 2.18 (3H, s), 2.19 (3H, s), 2.23 (2H, s), 2.63 (1H, brs), 6.81 (1H, brs), 6.94-7.01 (2H, m), 7.29-7.32 (2H, m).

[0200]

Reference Example 155

N-(3-Benzyl-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and commercially available benzylmagnesium chloride, the title compound was synthesized in the same manner as in Reference Example 145. Yield: 88%. Melting point: 212 - 213°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.08 (9H, s), 1.31 (3H, s), 1.43 (3H, s), 1.75 (1H, s), 2.09-2.17 (8H, m), 3.02 (1H, d, J = 13.6 Hz), 3.16 (1H, d, J = 13.6 Hz), 6.56 (1H, s), 6.66 (1H, brs), 7.20-7.38 (5H, m).

[0201]

Reference Example 156

N-(3-Hydroxy-3-(4-isopropylbenzyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

5 Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and 4-isopropylbenzyl chloride, the title compound was synthesized in the same manner as in Reference Example 146. Yield: 94%. Melting point: 177 - 178°C

10 (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.10 (9H, s), 1.25 (6H, d, $J = 6.9$ Hz), 1.33 (3H, s), 1.43 (3H, s), 2.04 (1H, s), 2.11 (3H, s), 2.14 (3H, s), 2.19 (2H, m), 2.90 (1H, septet, $J = 6.9$ Hz), 3.00 (1H, d, $J = 13.6$ Hz), 3.13 (1H, d, $J = 13.6$ Hz), 6.66

15 (2H, brs), 7.15 (2H, d, $J = 8.0$ Hz), 7.24 (2H, d, $J = 8.0$ Hz).

[0202]

Reference Example 157

N-(3-Butyl-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

20

 Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and commercially available n-butyllithium, the title compound was synthesized in the same manner as in

25 Reference Example 147. Yield: 78%. Melting point: 161 -

162°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.91 (3H, t, J = 7.2 Hz), 1.13 (9H, s),
1.30-1.43 (6H, m), 1.49 (3H, s), 1.60-1.79 (3H, m), 1.90-
1.99 (1H, m), 2.13 (6H, s), 2.24 (2H, s), 6.77 (1H, brs),
5 7.23 (1H, s).

[0203]

Reference Example 158

N-(3-(2-Furyl)-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

10 Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and furan, the title compound was synthesized in the same manner as in Reference Example 147. Yield: 88%.
Melting point: 108 - 110°C (ethyl acetate - hexane).

15 ¹H-NMR (CDCl₃) δ: 0.96 (3H, s), 1.13 (9H, s), 1.59 (3H, s), 2.17 (3H, s), 2.18 (3H, s), 2.24 (2H, s), 2.59 (1H, brs), 6.35-6.37 (2H, m), 6.79 (1H, brs), 7.37 (1H, s), 7.43 (1H, s).

[0204]

20 Reference Example 159

N-(3-(2,4-Dimethoxyphenyl)-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference
25 Example 65 and 1-bromo-2,4-dimethoxybenzene, the title

compound was synthesized in the same manner as in Reference Example 146. Yield: 62%. Melting point: 150 - 151°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.91 (3H, s), 1.10 (9H, s), 1.65 (3H, s),
5 2.12-2.20 (8H, m), 3.79 (3H, s), 3.91 (3H, s), 5.03 (1H, brs), 6.43 (1H, dd, J = 8.4, 2.4 Hz), 6.52 (1H, d, J = 2.4 Hz), 6.92 (1H, brs), 7.05-7.08 (2H, m).

[0205]

Reference Example 160

10 N-(3-(4-Bromophenyl)-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and 1,4-dibromobenzene, the title compound was
15 synthesized in the same manner as in Reference Example 147. Yield: 93%. Melting point: 118 - 119°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.86 (3H, s), 1.10 (9H, s), 1.56 (3H, s),
2.17-2.22 (8H, m), 2.44 (1H, brs), 6.80 (1H, brs), 7.10 (1H, s),
20 7.36 (2H, d, J = 8.4 Hz), 7.48 (2H, d, J = 8.4 Hz).

[0206]

Reference Example 161

N-(3-Hydroxy-3-(4-methoxyphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

25 Using 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-

dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 65 and 1-bromo-4-methoxybenzene, the title compound was synthesized in the same manner as in Reference Example 146. Yield: 72%. Melting point: 110 - 111°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.84 (3H, s), 1.11 (9H, s), 1.58 (3H, s), 2.18-2.24 (9H, m), 3.81 (3H, s), 6.78 (1H, brs), 6.88 (2H, d, J = 9.0 Hz), 7.12 (1H, s), 7.40 (2H, d, J = 9.0 Hz).

[0207]

10 Reference Example 162

N-(3-Cyclohexyl-3-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,4,6,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 63 and commercially available cyclohexylmagnesium bromide, the title compound was synthesized in the same manner as in Reference Example 145. Yield: 66%. Melting point: 170 - 171°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.60-2.10 (30H, m), 2.12 (3H, s), 2.20-2.40 (5H, m), 6.55 (1H, br s).

[0208]

Reference Example 163

N-(3-Hydroxy-2,2,4,6,7-pentamethyl-3-(2-pyridyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

25 Using 3,3-dimethyl-N-(2,2,4,6,7-pentamethyl-3-oxo-2,3-

dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 63 and 2-bromopyridine, the title compound was synthesized in the same manner as in Reference Example 147. Yield: 45%. Melting point: 205 - 207°C.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 0.89 (3H, s), 1.12 (9H, s), 1.53 (3H, s), 1.64 (3H, s), 2.13 (3H, s), 2.14 (3H, s), 2.25 (2H, s), 6.01 (1H, br s), 6.85 (1H, br s), 7.06 (1H, d, $J = 6.0$ Hz), 7.18-7.24 (1H, m), 7.60 (1H, dt, $J = 7.8, 1.8$ Hz), 8.56 (1H, dd, $J = 7.8, 4.8$ Hz).

10 [0209]

Reference Example 164

N-(3-Hydroxy-3-(4-methoxyphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

15 Using 3,3-dimethyl-N-(2,2,4,6,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 63 and 4-bromoanisole, the title compound was synthesized in the same manner as in Reference Example 147. Yield: 47%. Melting point: 98 - 99°C (ethyl acetate - hexane).

20 $^1\text{H-NMR}$ (CDCl_3) δ : 0.86 (3H, s), 1.13 (9H, s), 1.51 (3H, s), 1.85 (3H, s), 2.15 (3H, s), 2.16 (3H, s), 2.27 (2H, s), 3.79 (3H, s), 6.59 (1H, br), 6.83 (3H, br), 7.38 (1H, br).

[0210]

Reference Example 165

25 N-(3-Hydroxy-3-(3-methoxyphenyl)-2,2,4,6,7-pentamethyl-2,3-

dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,4,6,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide obtained in Reference Example 63 and 3-bromoanisole, the title compound was

5 synthesized in the same manner as in Reference Example 147.

Yield: 46%. Melting point: 154 - 155°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.89 (3H, s), 1.13 (9H, s), 1.52 (3H, s), 1.87 (3H, s), 2.16 (3H, s), 2.17 (3H, s), 2.27 (2H, s),
10 3.80 (3H, brs), 6.45 (1H, br), 6.53 (1H, s), 6.75-6.84 (1H, m), 7.20 (2H, br).

[0211]

Reference Example 166

N-(3-Hydroxy-3-(4-isopropylphenyl)-2,2,4,5,6-pentamethyl-
15 2,3-dihydro-1-benzofuran-7-yl)-3,3-dimethylbutanamide

Using 3,3-dimethyl-N-(2,2,4,5,6-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-7-yl)butanamide obtained in Reference Example 64 and 1-bromo-4-isopropylbenzene, the title compound was synthesized in the same manner as in Reference
20 Example 146. Yield: 71%. Melting point: 178 - 179°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.82 (3H, s), 1.14 (9H, s), 1.24 (6H, d, J = 6.9 Hz), 1.49 (3H, s), 1.91 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 2.29 (2H, s), 2.35 (1H, s), 2.89 (1H, septet, J =
25 6.9 Hz), 6.40-7.80 (5H, m).

[0212]

Reference Example 167

tert-Butyl (3-hydroxy-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)carbamate

5 Using tert-butyl (2,2,4,6,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 62 and 1-bromo-4-methylbenzene, the title compound was synthesized in the same manner as in Reference Example 147. Yield: 64%. Amorphous powder.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 0.85 (3H, s), 1.20-1.60 (9H, m), 1.50 (3H, s), 1.88 (3H, s), 2.15 (3H, s), 2.19 (3H, s), 2.34 (3H, s), 5.77 (1H, br s), 6.40-8.20 (4H, m), 1H unidentified.

[0213]

Reference Example 168

15 tert-Butyl (3-hydroxy-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate

 Using tert-butyl (2,2,4,6,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 62 and 1-iodo-4-isopropylbenzene, the title

20 compound was synthesized in the same manner as in Reference Example 147. Yield: 34%. Melting point: 155 - 157°C (hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.85 (3H, s), 1.24 (6H, d, $J = 7.0$ Hz), 1.20-1.64 (9H, m), 1.52 (3H, s), 1.89 (3H, s), 2.08 (1H, s),
25 2.16 (3H, s), 2.20 (3H, s), 2.74-3.06 (1H, m), 5.75 (1H, br

s), 6.40-8.20 (4H, m).

[0214]

Reference Example 169

tert-Butyl (3-hydroxy-2,2,4,6,7-pentamethyl-3-(2-naphthyl)-
5 2,3-dihydro-1-benzofuran-5-yl)carbamate

Using tert-butyl (2,2,4,6,7-pentamethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 62 and 2-bromonaphthalene, the title compound was synthesized in the same manner as in Reference Example 147.

10 Yield: 50%. Amorphous powder.

¹H-NMR (CDCl₃) δ: 0.90 (3H, br s), 1.20-1.70 (9H, m), 1.57 (3H, s), 1.86 (3H, br s), 2.19 (3H, s), 2.22 (3H, s), 2.29 (1H, s), 5.77 (1H, br s), 6.60-8.60 (7H, m).

[0215]

15 Reference Example 170

N-(3-(3-Formylphenyl)-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of 2-(3-bromophenyl)-1,3-dioxolane (1.65 mL, 10.9 mmol) in THF (20 mL) was added dropwise at -78°C
20 under an argon atmosphere n-butyllithium (1.59 M hexane solution, 6.4 mL, 10.2 mmol), and the resulting mixture was stirred for 30 minutes. To the reaction solution was added dropwise at -78°C a solution of 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide
25 (1.0 g, 3.30 mmol) obtained in Reference Example 65 in THF

(10 mL), and the resulting mixture was stirred for 30 minutes. The reaction solution was warmed to room temperature and stirred for 1 hour, and water was added to the reaction solution and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate - hexane 5 : 95 - 40 : 60) to obtain 1.38 g (yield: 92%) of N-(3-(3-(1,3-dioxolan-2-yl)phenyl)-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide as an amorphous powder. To a mixed solution of the obtained N-(3-(3-(1,3-dioxolan-2-yl)phenyl)-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (300 mg, 0.66 mmol) in acetone (4 mL) - water (0.3 mL) was added pyridinium p-toluenesulfonate (5 mg, 0.03 mmol), and the mixture was stirred for 30 minutes. The reaction solution was cooled to room temperature, and water was added to the reaction solution and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was recrystallized from THF - diisopropyl ether to obtain 194 mg (yield: 72%) of the title compound. Melting point: 189 - 190°C.

¹H-NMR (CDCl₃) δ: 0.86 (3H, s), 1.09 (9H, s), 1.59 (3H, s), 2.18-2.22 (8H, m), 2.66 (1H, s), 6.86 (1H, br s), 7.11 (1H, s), 7.52 (1H, t, J = 7.5 Hz), 7.76 (1H, d, J = 7.5 Hz), 7.84 (1H, d, J = 7.5 Hz), 7.99 (1H, s), 10.01 (1H, s).

5 [0216]

Reference Example 171

N-(3-Hydroxy-3-(3-(hydroxymethyl)phenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

10 Using N-(3-(3-formylphenyl)-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 167, the title compound was obtained in the same manner as in Example 21. Yield: 86%. Melting point: 169 - 171°C (THF -
15 diisopropyl ether).

¹H-NMR (CDCl₃) δ: 0.85 (3H, s), 1.09 (9H, s), 1.60 (3H, s), 1.65 (1H, brs), 2.17-2.20 (8H, m), 2.41 (1H, br s), 4.60 (2H, s), 6.85 (1H, br s), 7.10 (1H, s), 7.25-7.42 (3H, m), 7.49 (1H, s).

20 [0217]

Reference Example 172

N-(3-Hydroxy-3-(3-(1-hydroxyethyl)phenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

25 Using N-(3-(3-formylphenyl)-3-hydroxy-2,2,6,7-

tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 65 and methylmagnesium bromide, the title compound was synthesized in the same manner as in Example 22. Yield: 43%. Melting point: 206 - 207°C (THF - diisopropyl ether).

¹H-NMR (CDCl₃) δ: 0.85 (3H, s), 1.09 (9H, s), 1.46-1.49 (3H, m), 1.60 (3H, s), 2.17-2.21 (9H, m), 2.27 (1H, brs), 4.88 (1H, br s), 6.80 (1H, s), 7.14 (1H, s), 7.30-7.45 (3H, m), 7.52 (1H, s).

10 [0218]

Reference Example 173

N-(3-Hydroxy-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 5-amino-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-3-ol obtained in Reference Example 83, the title compound was synthesized in the same manner as in Reference Example 63. Yield: 59%. Melting point: 146 - 148°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.86 (3H, s), 1.12 (9H, s), 1.51 (3H, s), 1.71 (1H, s), 1.85 (3H, s), 2.16 (6H, s), 2.27 (2H, s), 2.33 (3H, s), 6.60 (1H, br s), 6.82-7.80 (4H, m).

[0219]

Reference Example 174

N-(3-Hydroxy-2,2,4,6,7-pentamethyl-3-(2-naphthyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 5-amino-2,2,4,6,7-pentamethyl-3-(2-naphthyl)-
2,3-dihydro-1-benzofuran-3-ol obtained in Reference Example
84, the title compound was synthesized in the same manner
as in Reference Example 63. Yield: 82%. Amorphous powder.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 0.90 (3H, br. s), 1.11 (9H, s), 1.58 (3H,
s), 1.83 (3H, br. s), 2.19 (6H, s), 2.26 (2H, s), 2.38 (1H,
br. s), 6.40-8.60 (7H, m), 6.60 (1H, br s).

[0220]

Reference Example 175

10 N-(3-Hydroxy-2,2,4,6,7-pentamethyl-3-(2-naphthyl)-2,3-
dihydro-1-benzofuran-5-yl)-3-methylbutanamide

Using 5-amino-2,2,4,6,7-pentamethyl-3-(2-naphthyl)-
2,3-dihydro-1-benzofuran-3-ol obtained in Reference Example
84 and 3-methylbutyryl chloride, the title compound was
15 synthesized in the same manner as in Reference Example 63.
Yield: 32%. Melting point: 108 - 110°C (ethyl acetate -
hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.80-1.10 (9H, m), 1.50-1.95 (7H, m),
2.05-2.80 (9H, m), 6.65 (1H, br s), 7.00-8.32 (7H, m).

20 [0221]

Reference Example 176

N-(tert-Butyl)-N'-(3-hydroxy-2,2,4,6,7-pentamethyl-3-(2-
naphthyl)-2,3-dihydro-1-benzofuran-5-yl)urea

Using 5-amino-2,2,4,6,7-pentamethyl-3-(2-naphthyl)-
25 2,3-dihydro-1-benzofuran-3-ol obtained in Reference Example

84, the title compound was synthesized in the same manner as in Example 14. Yield: 74%. Melting point: 212 - 214°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.92 (3H, br s), 1.27 (9H, s), 1.60 (3H, s), 1.88 (3H, br s), 2.21 (3H, s), 2.23 (3H, s), 2.44 (1H, br s), 4.12 (1H, br s), 5.33 (1H, br. s), 6.60-8.60 (7H, m).

[0222]

Reference Example 177

3,3-Dimethyl-N-(2,2,6,7-tetramethyl-3-(2-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)butanamide

To a solution of N-(3-hydroxy-2,2,6,7-tetramethyl-3-(2-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (120 mg, 0.3 mmol) obtained in Example 148 in trifluoroacetic acid (2 mL) was added triethylsilane (71 mg, 0.6 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hour. The reaction solution was added to water and the product was extracted with ethyl acetate. The organic layer was washed with an aqueous 1 N sodium hydroxide solution, water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate - hexane 5 : 95 - 35 : 65) and recrystallized from ethyl acetate - hexane to obtain 93 mg (yield: 79%) of the title compound. Melting point: 161 - 162°C.

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.09 (9H, s), 1.56 (3H, s), 2.15-2.19 (8H, m), 2.39 (3H, s), 4.57 (1H, s), 6.60-6.75 (2H, m), 6.91 (1H, s), 7.00-7.18 (3H, m).

[0223]

5 Reference Example 178

3,3-Dimethyl-N-(2,2,6,7-tetramethyl-3-(3-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)butanamide

Using N-(3-hydroxy-2,2,6,7-tetramethyl-3-(3-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-

10 dimethylbutanamide obtained in Example 145, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 87%. Melting point: 156 - 157°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.96 (3H, s), 1.09 (9H, s), 1.55 (3H, s), 15 2.15-2.19 (8H, m), 2.31 (3H, s), 4.27 (1H, s), 6.70 (1H, br s), 6.85-6.92 (3H, m), 7.04 (1H, d, J = 8.4 Hz), 7.16 (1H, t, J = 8.4 Hz).

[0224]

Reference Example 179

20 N-(3-(3-Isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-hydroxy-3-(3-isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-

25 dimethylbutanamide obtained in Reference Example 151, the title compound was synthesized in the same manner as in

Reference Example 177. Yield: 65%. Melting point: 162 - 163°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.93 (3H, s), 1.09 (9H, s), 1.22 (6H, d, J = 6.9 Hz), 1.57 (3H, s), 2.15-2.20 (8H, m), 2.86 (1H, septet, J = 6.9 Hz), 4.32 (1H, s), 6.72 (1H, br s), 6.90-7.09 (3H, m), 7.08-7.25 (2H, m).

[0225]

Reference Example 180

N-(2,2,6,7-Tetramethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-hydroxy-2,2,6,7-tetramethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 149, the title compound was synthesized in the same manner as in Reference Example 177.

Yield: 82%. Melting point: 182 - 183°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.09 (9H, s), 1.57 (3H, s), 2.15-2.20 (8H, m), 4.32 (1H, s), 6.72 (1H, br s), 6.95 (1H, s), 7.06-7.11 (2H, m), 7.23-7.31 (3H, m).

[0226]

Reference Example 181

N-(2,2,6,7-Tetramethyl-3-(2-naphthyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-hydroxy-2,2,6,7-tetramethyl-3-(2-naphthyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

obtained in Reference Example 150, the title compound of an oily matter was obtained in the same manner as in Reference Example 177. Yield: 84%.

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.06 (9H, s), 1.60 (3H, s),
5 2.16-2.22 (8H, m), 4.47 (1H, s), 6.77 (1H, brs), 6.93 (1H, s), 7.18 (1H, dd, J = 8.6, 1.6 Hz), 7.42-7.49 (2H, m), 7.58 (1H, br s), 7.73-7.82 (3H, m).

[0227]

Reference Example 182

10 N-(3-(2-Methoxyphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-hydroxy-3-(2-methoxyphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 152, the
15 title compound was synthesized in the same manner as in Reference Example 177. Yield: 82%. Melting point: 169 - 170°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.97 (3H, s), 1.10 (9H, s), 1.57 (3H, s),
2.15-2.19 (8H, m), 3.85 (3H, s), 4.82 (1H, s), 6.72 (1H, br
20 s), 6.75-6.91 (4H, m), 7.15-7.26 (1H, m).

[0228]

Reference Example 183

N-(3-Benzyl-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

25 Using N-(3-benzyl-3-hydroxy-2,2,6,7-tetramethyl-2,3-

dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 155, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 56%. Melting point: 186 - 187°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.08 (9H, s), 1.33 (3H, s), 1.37 (3H, s), 2.09 (3H, s), 2.12 (3H, s), 2.17 (2H, s), 2.89 (2H, d, J = 7.8 Hz), 3.42 (1H, t, J = 7.8 Hz), 6.49 (1H, s), 6.62 (1H, br s), 7.17-7.33 (5H, m).

[0229]

Reference Example 184

N-(3-(4-Isopropylbenzyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-hydroxy-3-(4-isopropylbenzyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 156, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 63%. Melting point: 130 - 132°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.10 (9H, s), 1.25 (6H, d, J = 6.9 Hz), 1.33 (3H, s), 1.43 (3H, s), 2.04 (1H, s), 2.11 (3H, s), 2.14 (3H, s), 2.19 (2H, m), 2.86 (1H, septet, J = 6.9 Hz), 3.00 (1H, d, J = 13.6 Hz), 3.13 (1H, d, J = 13.6 Hz), 6.66 (2H, br s), 7.15 (2H, d, J = 8.0 Hz), 7.24 (2H, d, J = 8.0 Hz).

[0230]

Reference Example 185

N-(2,2,6,7-Tetramethyl-3-(2-thienyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

5 Using N-(3-hydroxy-2,2,6,7-tetramethyl-3-(2-thienyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 154, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 65%. Melting point: 137 - 138°C (ethyl acetate -
10 hexane).

¹H-NMR (CDCl₃) δ: 1.05 (3H, s), 1.10 (9H, s), 1.58 (3H, s), 2.15-2.21 (8H, m), 4.61 (1H, s), 6.77 (1H, br s), 6.85 (1H, d, J = 3.4 Hz), 6.97 (1H, dd, J = 4.8, 3.4 Hz), 7.10 (1H, s), 7.19 (1H, d, J = 4.8 Hz).

15 [0231]

Reference Example 186

N-(2,2,6,7-Tetramethyl-3-(2-(trifluoromethoxy)phenyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

20 Using N-(3-hydroxy-2,2,6,7-tetramethyl-3-(2-(trifluoromethoxy)phenyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 147, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 47%. Melting point: 155 - 156°C (ethyl acetate - hexane).

25 ¹H-NMR (CDCl₃) δ: 0.97 (3H, s), 1.11 (9H, s), 1.62 (3H, s),

2.18 (6H, s), 2.22 (2H, s), 3.00 (1H, br s), 6.79 (1H, br s), 7.15-7.36 (5H, m).

[0232]

Reference Example 187

5 N-(3-Butyl-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-butyl-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 157, the title compound was
10 synthesized in the same manner as in Reference Example 177. Yield: 77%. Melting point: 129 - 130°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.91 (3H, t, J = 7.2 Hz), 1.13 (9H, s), 1.30-1.43 (6H, m), 1.49 (3H, s), 1.60-1.79 (3H, m), 1.90-
15 1.99 (1H, m), 2.13 (6H, s), 2.24 (2H, s), 6.77 (1H, br s), 7.23 (1H, s).

[0233]

Reference Example 188

N-(3-(2-Furyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-
20 benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-(2-furyl)-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 158, the title compound was synthesized in the same manner as in Reference Example 177.
25 Yield: 67%. Melting point: 126 - 127°C (ethyl acetate -

hexane).

¹H-NMR (CDCl₃) δ: 1.06 (3H, s), 1.12 (9H, s), 1.59 (3H, s),
2.12-2.22 (8H, m), 4.44 (1H, s), 6.10 (1H, d, J = 3.2 Hz),
6.30-6.33 (1H, m), 6.74 (1H, br s), 7.10 (1H, s), 7.35-7.36
5 (1H, m).

[0234]

Reference Example 189

N-(2,2,6,7-Tetramethyl-3-(2-phenylethyl)-2,3-dihydro-1-
benzofuran-5-yl)-3,3-dimethylbutanamide

10 Using N-(3-hydroxy-2,2,6,7-tetramethyl-3-(2-
phenylethyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-
dimethylbutanamide obtained in Reference Example 146, the
title compound was synthesized in the same manner as in
Reference Example 177. Yield: 92%. Melting point: 158 -
15 159°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.13 (9H, s), 1.37 (3H, s), 1.45 (3H, s),
1.86-1.96 (2H, m), 2.12 (6H, s), 2.33 (2H, s), 2.65-2.83
(2H, m), 3.03 (1H, t, J = 7.8 Hz), 6.73 (1H, br s), 7.17-
7.31 (6H, m).

20 [0235]

Reference Example 190

N-(3-(4-Bromophenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-
benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-(4-bromophenyl)-3-hydroxy-2,2,6,7-
25 tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-

dimethylbutanamide obtained in Reference Example 160, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 88%. Melting point: 171 - 172°C (ethyl acetate - hexane).

5 $^1\text{H-NMR}$ (CDCl_3) δ : 0.95 (3H, s), 1.10 (9H, s), 1.54 (3H, s), 2.15 (3H, s), 2.18 (3H, s), 2.20 (2H, s), 4.28 (1H, s), 6.72 (1H, br s), 6.94-6.98 (3H, m), 7.41 (2H, d, $J = 8.4$ Hz).

[0236]

10 Reference Example 191

N-(3-(4-Methoxyphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-hydroxy-3-(4-methoxyphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-

15 dimethylbutanamide obtained in Reference Example 161, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 82%. Melting point: 169 - 170°C (ethyl acetate - hexane).

20 $^1\text{H-NMR}$ (CDCl_3) δ : 0.95 (3H, s), 1.10 (9H, s), 1.54 (3H, s), 2.14-2.20 (8H, m), 3.79 (3H, s), 4.27 (1H, s), 6.71 (1H, br s), 6.82 (2H, d, $J = 8.7$ Hz), 6.93 (1H, s), 7.01 (2H, d, $J = 8.7$ Hz).

[0237]

Reference Example 192

25 N-(3-(2,4-(Dimethoxyphenyl)-2,2,6,7-tetramethyl-2,3-

dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-(2,4-(dimethoxyphenyl)-3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 159, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 82%. Melting point: 146 - 147°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.97 (3H, s), 1.09 (9H, s), 1.55 (3H, s), 2.14-2.19 (8H, m), 3.78 (3H, s), 3.82 (3H, s), 4.73 (1H, s), 6.35 (1H, dd, J = 8.4, 2.4 Hz), 6.45 (1H, d, J = 2.4 Hz), 6.66 (1H, d, J = 8.4 Hz), 6.76 (1H, br s), 6.90 (1H, s).

[0238]

Reference Example 193

N-(3-Cyclohexyl-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-cyclohexyl-3-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 162, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 48%. Melting point: 198 - 199°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.50-2.20 (35H, m), 2.24-2.35 (2H, m), 2.67 (1H, d, J = 2.7 Hz), 6.55 (1H, br s).

[0239]

Reference Example 194

3,3-Dimethyl-N-(2,2,4,6,7-pentamethyl-3-(2-pyridyl)-2,3-dihydro-1-benzofuran-5-yl)butanamide

Using N-(3-hydroxy-2,2,4,6,7-pentamethyl-3-(2-pyridyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-

5 dimethylbutanamide obtained in Reference Example 163, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 52%. Melting point: 210 - 212°C.

¹H-NMR (CDCl₃) δ: 1.04 (3H, s), 1.12 (9H, s), 1.55 (3H, s),
10 1.79 (3H, s), 2.17 (6H, s), 2.26 (2H, s), 4.41 (1H, s),
6.52 (1H, br s), 6.78 (1H, d, J = 7.6 Hz), 7.12 (1H, dd, J
= 7.6, 4.4 Hz), 7.54-7.61 (1H, m), 8.53 (1H, d, J = 4.4 Hz).

[0240]

Reference Example 195

15 N-(3-(4-Methoxyphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-hydroxy-3-(4-methoxyphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-

20 dimethylbutanamide obtained in Reference Example 164, the title compound was synthesized in the same manner as in Reference Example 177. Yield: 40%. Melting point: 175 - 176°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.12 (9H, s), 1.48 (3H, s),
1.77 (3H, s), 2.15 (6H, s), 2.24 (2H, s), 3.76 (3H, s), 4.08
25 (1H, s), 6.48 (1H, s), 6.76 (1H, br d, J = 5.4 Hz), 6.83

(2H, br).

[0241]

Reference Example 196

N-(3-(3-Methoxyphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-
5 benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-hydroxy-3-(3-methoxyphenyl)-2,2,4,6,7-
pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-
dimethylbutanamide obtained in Reference Example 165, the
title compound was synthesized in the same manner as in
10 Reference Example 177. Yield: 77%. Melting point: 166 -
167°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.04 (3H, s), 1.12 (9H, s), 1.49 (3H, s),
1.79 (3H, s), 2.15 (6H, s), 2.25 (2H, s), 3.76 (3H, s), 4.09
(1H, s), 6.25 (1H, br), 6.47 (1H, s), 6.60-6.85 (2H, m),
15 7.08 (1H, br).

[0242]

Reference Example 197

N-(3-(4-Isopropylphenyl)-2,2,4,5,6-pentamethyl-2,3-dihydro-
1-benzofuran-7-yl)-3,3-dimethylbutanamide

Using N-(3-hydroxy-3-(4-isopropylphenyl)-2,2,4,5,6-
20 pentamethyl-2,3-dihydro-1-benzofuran-7-yl)-3,3-
dimethylbutanamide obtained in Reference Example 166, the
title compound was synthesized in the same manner as in
Reference Example 177. Yield: 53%. Melting point: 152 -
25 153°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.97 (3H, s), 1.14 (9H, s), 1.21 (6H, d, J = 6.9 Hz), 1.46 (3H, s), 1.83 (3H, s), 2.08 (3H, s), 2.17 (3H, s), 2.29 (2H, s), 2.85 (1H, septet, J = 6.9 Hz), 4.11 (1H, s), 6.40-7.15 (5H, m).

5 [0243]

Reference Example 198

N-(3-(4-Formylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of N-(3-(4-bromophenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (500 mg, 1.13 mmol) obtained in Reference Example 190 in THF (10 mL) was added dropwise at -78°C under an argon atmosphere n-butyllithium (1.59 M hexane solution, 1.56 mL, 2.48 mmol), and the mixture was stirred for 30 minutes. DMF (90 mg, 1.24 mmol) was added to the reaction solution at the same temperature, and the mixture was stirred for 30 minutes, warmed to room temperature, and stirred for 1 hour. Water was added to the reaction solution and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate - hexane 5 : 95 - 45 : 55) and recrystallized from ethyl acetate - hexane to obtain 204 mg (yield: 46%) of the title

compound. Melting point: 169 - 170°C.

¹H-NMR (CDCl₃) δ: 0.97 (3H, s), 1.09 (9H, s), 1.58 (3H, s),
2.04-2.20 (8H, m), 4.38 (1H, s), 6.74 (1H, br s), 6.99 (1H,
s), 7.25 (2H, d, J = 8.4 Hz), 7.81 (2H, dd, J = 8.4 Hz),
5 9.99 (1H, s).

[0244]

Reference Example 199

N-(3-(4-Acetylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

10 Using N-(3-(4-bromophenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 190 and N,N-dimethylacetamide, the title compound was synthesized in the same manner as in Reference Example 198. Yield: 20%. Melting point: 195 -
15 196°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.96 (3H, s), 1.09 (9H, s), 1.57 (3H, s),
2.16-2.19 (8H, m), 2.59 (3H, s), 4.36 (1H, s), 6.73 (1H, br
s), 6.97 (1H, s), 7.18 (2H, d, J = 8.0 Hz), 7.88 (2H, d, J
= 8.0 Hz).

20 [0245]

Reference Example 200

N-(3-(4-(Hydroxymethyl)phenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-(4-formylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained
25

in Reference Example 198, the title compound was synthesized in the same manner as in Example 21. Yield: 80%. Melting point: 162 - 163°C (THF - diisopropyl ether). ¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.09 (9H, s), 1.56 (3H, s), 1.65 (1H, t, J = 6.0 Hz), 2.15-2.19 (8H, m), 4.32 (1H, s), 4.67 (2H, d, J = 6.0 Hz), 6.72 (1H, br s), 6.94 (1H, s), 7.09 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.0 Hz).

[0246]

Reference Example 201

10 N-(3-(4-(1-Hydroxyethyl)phenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(3-(4-acetylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 199, the title compound of an oily matter was synthesized in the same manner as in Example 21. Yield: 65%.

¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.09 (9H, s), 1.48 (3H, d, J = 6.4 Hz), 1.55 (3H, s), 1.66 (1H, brs), 2.14-2.19 (8H, m), 4.30 (1H, s), 4.87 (1H, q, J = 6.4 Hz), 6.79 (1H, br s), 6.93 (1H, s), 7.07 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.0 Hz).

[0247]

Reference Example 202

25 N-(3-(2-Isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

A solution of 1-bromo-2-isopropylbenzene (1.20 g, 6.03 mmol) in THF (5 mL) was added dropwise under an argon atmosphere to a mixture of magnesium (147 mg, 6.03 mmol) and a catalytic amount of iodine, and the mixture was stirred at 70°C for 30 minutes. To the reaction solution was added dropwise a solution of 3,3-dimethyl-N-(2,2,6,7-tetramethyl-3-oxo-2,3-dihydro-1-benzofuran-5-yl)butanamide (350 mg, 1.15 mmol) obtained in Reference Example 65 in THF (3 mL), and the mixture was refluxed with heating for 12 hours. The reaction solution was added to ice and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 2) to obtain 79 mg (yield: 16%) of N-(3-hydroxy-3-(3-isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide. To a solution of N-(3-hydroxy-3-(3-isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (79 mg, 0.19 mmol) in trifluoroacetic acid (1 mL) was added with ice-cooling triethylsilane (44 mg, 0.38 mmol), and the mixture was stirred at room temperature for 1 hour. The reaction solution was added to water and the product was extracted with ethyl acetate. The organic layer was washed

with an aqueous 1 N sodium hydroxide solution, water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl

5 acetate : hexane = 1 : 2) to obtain 39 mg (yield: 51%) of the title compound. Yield: 51%. Melting point: 188 - 189°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.01 (3H, s), 1.09 (9H, s), 1.27 (3H, d, J = 7.0 Hz), 1.32 (3H, d, J = 7.0 Hz), 1.57 (3H, s), 2.15-
10 2.20 (8H, m), 3.15-3.30 (1H, m), 4.67 (1H, s), 6.67 (1H, d, J = 7.8 Hz), 6.69 (1H, br s), 6.88 (1H, s), 7.02 (1H, t, J = 7.8 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.29 (1H, d, J = 7.8 Hz).

[0248]

15 Reference Example 203

3,3-Dimethyl-N-(2,2,4,6,7-pentamethyl-3-piperidin-1-yl-2,3-dihydro-1-benzofuran-5-yl)butanamide

To a solution of N-(3-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (450
20 mg, 1.41 mmol) obtained in Reference Example 66 in dichloromethane (3 mL) was added triethylamine (0.79 mL, 5.64 mmol), and then added dropwise with ice-cooling methanesulfonyl chloride (0.22 mL, 2.82 mmol). The
reaction solution was stirred for 30 minutes, and to the
25 reaction solution was added piperidine (0.70 mL, 7.05 mmol),

and the mixture was stirred at room temperature for 16 hours. Water was added to the reaction solution and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 20 : 1) to obtain 270 mg (yield: 50%) of the title compound. Melting point: 229 - 230°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.10-1.82 (22H, m), 2.08 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 2.22-2.43 (3H, m), 2.78 (1H, br s), 2.95 (1H, br s), 3.68 (1H, s), 6.56 (1H, s)

[0249]

Reference Example 204

3,3-Dimethyl-N-(2,2,4,6,7-pentamethyl-3-pyrrolidin-1-yl-2,3-dihydro-1-benzofuran-5-yl)butanamide

Using N-(3-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 66 and pyrrolidine, the title compound was synthesized in the same manner as in Reference Example 203. Yield: 36%. Melting point: 197 - 198°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.16 (9H, s), 1.23 (3H, s), 1.49 (3H, s), 1.58-1.72 (4H, m), 2.09 (3H, s), 2.13 (6H, s), 2.30 (2H, s), 2.48-2.80 (4H, m), 4.02 (1H, s), 6.55 (1H, br s).

[0250]

Reference Example 205

N-(3-Anilino-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

5 Using N-(3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 67 and aniline, the title compound was synthesized in the same manner as in Reference Example 203. Yield: 79%. Melting point: 151 - 152°C (ethyl acetate -
10 hexane).

¹H-NMR (CDCl₃) δ: 1.11 (9H, s), 1.37 (3H, s), 1.53 (3H, s), 2.14 (6H, s), 2.22 (2H, s), 3.93 (1H, d, J = 8.7 Hz), 4.81 (1H, d, J = 8.7 Hz), 6.60 (2H, d, J = 7.8 Hz), 6.67-6.75 (2H, m), 7.17 (3H, t, J = 7.8 Hz).

15 [0251]

Reference Example 206

N-(3-((2-Methoxyphenyl)amino)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

20 Using N-(3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 67 and (2-methoxyphenyl)amine, the title compound was synthesized in the same manner as in Reference Example 203. Yield: 75%. Melting point: 184 - 185°C (ethyl acetate - hexane).

25 ¹H-NMR (CDCl₃) δ: 1.11 (9H, s), 1.34 (3H, s), 1.53 (3H, s),

2.14 (6H, s), 2.22 (2H, s), 3.78 (3H, s), 4.53 (1H, d, J = 8.1 Hz), 4.86 (1H, d, J = 8.1 Hz), 6.63-6.68 (2H, m), 6.75-6.77 (2H, m), 6.86 (1H, t, J = 9.0 Hz), 7.16 (1H, s).

[0252]

5 Reference Example 207

N-(3-((2-(Trifluoromethoxy)phenyl)amino)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

10 Using N-(3-hydroxy-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Reference Example 67 and 2-trifluoromethoxyaniline, the title compound was synthesized in the same manner as in Reference Example 203. Yield: 73%. Melting point: 196 - 197°C (ethyl acetate - hexane).

15 ¹H-NMR (CDCl₃) δ: 1.11 (9H, s), 1.35 (3H, s), 1.54 (3H, s), 2.15 (6H, s), 2.23 (2H, s), 4.32 (1H, d, J = 9.0 Hz), 4.85 (1H, d, J = 9.0 Hz), 6.67 (1H, t, J = 6.9 Hz), 6.70-6.80 (2H, m), 7.12-7.17 (3H, m).

[0253]

20 Reference Example 208

tert-Butyl (7-bromo-2,2,4,6-tetramethyl-3-(pyrrolidin-1-yl)-2,3-dihydro-1-benzofuran-5-yl)carbamate

25 Using tert-butyl (7-bromo-3-hydroxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 69 and pyrrolidine, the title

compound was synthesized in the same manner as in Reference Example 203. Yield: 43%. Melting point: 128 - 130°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.28-1.57 (15H, m), 1.60-1.70 (4H, m),
5 2.14 (3H, s), 2.33 (3H, s), 2.40-2.67 (2H, m) 2.70-2.80 (2H, m), 4.13 (1H, s), 5.82 (1H, br s).

[0254]

Reference Example 209

tert-Butyl (7-bromo-3-(dimethylamino)-2,2,4,6-tetramethyl-
10 2,3-dihydro-1-benzofuran-5-yl)carbamate

Using tert-butyl (7-bromo-3-hydroxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 69 and dimethylamine, the title compound was synthesized in the same manner as in
15 Reference Example 203. Yield: 89%. Melting point: 111 - 112°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.27 (3H, s), 1.36-1.60 (12H, m), 2.04-2.60 (12H, m), 3.86 (1H, s), 5.84 (1H, br s).

[0255]

20 Reference Example 210

tert-Butyl (3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate

Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example
25 125, the title compound was synthesized in the same manner

as in Reference Example 59. Yield: 24%. Melting point:
119 - 120°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.21 (6H, d, J = 6.6 Hz),
1.25-1.58 (12H, m), 1.81 (3H, s), 2.16 (3H, s), 2.17 (3H,
5 s), 2.85 (1H, septet, J = 6.9 Hz), 4.08 (1H, s), 5.72 (1H,
s), 6.64-7.10 (4H, m).

[0256]

Reference Example 211

tert-Butyl (2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-
10 dihydro-1-benzofuran-5-yl)carbamate

Using 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-
dihydro-1-benzofuran-5-amine obtained in Reference Example
127, the title compound was synthesized in the same manner
as in Reference Example 59. Yield: 18%. Melting point:
15 124 - 125°C (hexane).

¹H-NMR (CDCl₃) δ: 1.01 (3H, s), 1.20-1.64 (9H, m), 1.48 (3H,
s), 1.80 (3H, s), 2.16 (3H, s), 2.17 (3H, s), 2.30 (3H, s),
4.08 (1H, s), 5.71 (1H, br s), 6.20-7.60 (4H, m).

[0257]

20 Reference Example 212

N-(7-(4-Isopropylbenzyl)-2,2,4,6-tetramethyl-2,3-dihydro-1-
benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of tert-butyl (7-bromo-2,2,4,6-
tetramethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate (1.77 g,
25 4.78 mmol) obtained in Reference Example 103 in THF (20 mL)

was added dropwise at -78°C under argon atmosphere *n*-butyllithium (1.60 M hexane solution, 6.25 mL, 10.0 mmol), and the mixture was stirred for 30 minutes. To the reaction solution was added dropwise at -78°C a solution of 4-isopropylbenzaldehyde (815 mg, 5.50 mmol) in THF (5 mL). The reaction solution was warmed to room temperature and stirred for 1 hour. Water was added to the reaction solution and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 4) to obtain 1.20 g (yield: 59%) of tert-butyl (7-(hydroxy(4-isopropylphenyl)methyl)-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate. To a mixture of the compound (1.00 g, 2.27 mmol) in trifluoroacetic acid (5 mL) was added with ice-cooling triethylsilane (1.0 mL, 6.4 mmol), and the mixture was stirred at room temperature for 1 hour. After the reaction solution was concentrated under reduced pressure, to the residue was added an aqueous saturated sodium hydrogen carbonate solution and the aqueous layer was made alkaline, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain

a crude product of 7-(4-isopropylbenzyl)-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-amine. To a solution of the compound (330 mg, about 1.02 mmol) and tert-butylacetyl chloride (0.16 mL, 1.12 mmol) in dichloromethane (30 mL) was added triethylamine (0.16 mL, 1.12 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction solution, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 1 N hydrochloric acid and an aqueous saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 273 mg (yield: 17%) of the title compound. Melting point: 170 - 171°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.13 (9H, s), 1.19 (6H, d, $J = 7.2$ Hz), 1.46 (6H, s), 2.05 (3H, s), 2.08 (3H, s), 2.25 (2H, s), 2.82 (1H, septet, $J = 7.2$ Hz), 2.96 (2H, s), 3.89 (2H, s), 6.46 (1H, br s), 7.04 (2H, d, $J = 8.1$ Hz), 7.09 (2H, d, $J = 8.1$ Hz).

[0258]

Reference Example 213

N-(7-(4-Isopropylbenzyl)-2,2,4,6-tetramethyl-3-(pyrrolidin-

1-yl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using tert-butyl (7-bromo-2,2,4,6-tetramethyl-3-(pyrrolidin-1-yl)-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 208, the title compound was synthesized in the same manner as in Reference Example 212. Yield: 61%. Melting point: 179 - 180°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.13 (9H, s), 1.18 (3H, s), 1.21 (3H, s), 1.25 (3H, s), 1.49 (3H, s), 1.62-1.72 (4H, m), 2.05 (3H, s), 2.14 (3H, s), 2.25 (2H, dd, J = 17.1, 13.2 Hz), 2.59 (2H, br), 2.70-2.90 (3H, m), 3.80-3.95 (2H, br), 4.05 (1H, s), 6.48 (1H, s), 7.00-7.10 (4H, m).

[0259]

Reference Example 214

N-(3-(Dimethylamino)-7-(4-isopropylbenzyl)-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using tert-butyl (7-bromo-3-(dimethylamino)-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate obtained in Reference Example 209, the title compound was synthesized in the same manner as in Reference Example 212. Yield: 33%. Melting point: 138 - 139°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.13 (9H, s), 1.18 (3H, s), 1.21 (3H, s), 1.24 (3H, s), 1.51 (3H, s), 2.03-2.06 (14H, m), 2.70-2.88

(1H, m), 3.78 (1H, s), 3.90 (2H, br s), 6.49 (1H, s), 6.98-7.05 (4H, m).

[0260]

Reference Example 215

5 (+)-N-((3R)-2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)-2-(4-(trifluoromethyl)phenyl)acetamide

To a DMF solution of (3R)-(+)-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained
10 in Reference Example 139 (0.89 g, 3 mmol), were added triethylamine (0.84 mL, 6 mmol), (4-(trifluoromethyl)phenyl)acetic acid (0.67 g, 3.3 mmol) and diethyl phosphorocyanidate (0.46 mL, 3.3 mmol) at 0°C, and the mixture was warmed to room temperature. After stirring
15 at the same temperature for 1 hour, the reaction solution was poured into cold water (50 mL). The precipitated crystals were taken, and the crystals were dissolved in ethyl acetate again. The organic layer was washed with a saturated sodium hydrogen carbonate solution and a
20 saturated brine, and then dried over anhydrous sodium sulfate. The solvent was dried under reduced pressure, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 1.19 g (yield 83%) of the title compound. Melting point:
25 187 - 189°C (diethyl ether - hexane).

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.47 (3H, s), 1.65 (3H, s), 2.04 (3H, s), 2.13 (3H, s), 2.29 (3H, s), 3.79 (2H, s), 4.06 (1H, s), 6.44 (1H, br), 7.02 (4H, br), 7.49 (2H, d, J = 8.2 Hz), 7.62 (2H, d, J = 8.2 Hz).

5 [0261]

Reference Example 216

(+)-2-(4-Methoxyphenyl)-N-((3R)-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)acetamide

Using (+)-(3R)-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 139 and 4-methoxyphenylacetic acid, the title compound was synthesized in the same manner as in Reference Example 215. Yield 74%. Melting point: 186 - 188°C (ethyl acetate - hexane).

15 ¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.46 (3H, s), 1.64 (3H, s), 2.04 (3H, s), 2.13 (3H, s), 2.28 (3H, s), 3.68 (2H, s), 3.80 (3H, s), 4.06 (1H, s), 6.44 (1H, br), 6.89 (2H, d, J = 8.6 Hz), 7.02 (4H, br), 7.25 (2H, d, J = 8.6 Hz).

[0262]

20 Reference Example 217

(+)-3-(4-Methoxyphenyl)-N-((3R)-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)propionamide

Using (+)-(3R)-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 139 and 4-methoxyphenylpropionic acid,

25

the title compound was synthesized in the same manner as in Reference Example 215. Yield 21%. Melting point: 170 - 172°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.48 (3H, s), 1.63 (3H, s),
5 1.99 (3H, s), 2.13 (3H, s), 2.29 (3H, s), 2.64 (2H, d, J = 7.4 Hz), 2.99 (2H, d, J = 7.4 Hz), 3.76 (3H, s), 4.08 (1H, s), 6.44 (1H, br), 6.81 (2H, d, J = 8.5 Hz), 7.02 (4H, br), 7.16 (2H, d, J = 8.5 Hz).

[0263]

10 Reference Example 218

3-(4-Methoxyphenyl)-N-(2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)propionamide

Using 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example
15 135 and 4-methoxyphenylpropionic acid, the title compound was synthesized in the same manner as in Reference Example 215. Yield 29%. Melting point: 180 - 183°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.48 (3H, s), 1.63 (3H, s),
20 1.99 (3H, s), 2.13 (3H, s), 2.29 (3H, s), 2.64 (2H, d, J = 7.3 Hz), 2.99 (2H, d, J = 7.3 Hz), 3.76 (3H, s), 4.08 (1H, s), 6.45 (1H, br), 6.81 (2H, d, J = 8.5 Hz), 7.02 (4H, br), 7.16 (2H, d, J = 8.5 Hz).

[0264]

25 Reference Example 219

2-(4-Methoxyphenyl)-N-(2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)acetamide

Using 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 135 and 4-methoxyphenylacetic acid, the title compound was synthesized in the same manner as in Reference Example 215. Yield 62%. Melting point: 166 - 167°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.46 (3H, s), 1.63 (3H, s), 2.03 (3H, s), 2.12 (3H, s), 2.28 (3H, s), 3.68 (2H, s), 3.79 (3H, s), 4.05 (1H, s), 6.43 (1H, br), 6.87 (2H, d, J = 8.6 Hz), 7.00 (4H, br), 7.25 (2H, d, J = 8.6 Hz).

[0265]

Reference Example 220

2-(4-Methoxyphenyl)-N-(2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)butanamide

Using 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 135 and 4-(4-methoxyphenyl)butanoic acid, the title compound was synthesized in the same manner as in Reference Example 215. Yield 11%. Melting point: 166 - 167°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.46 (3H, s), 1.63 (3H, s), 2.03 (3H, s), 2.12 (3H, s), 2.28 (3H, s), 3.68 (2H, s), 3.79 (3H, s), 4.05 (1H, s), 6.43 (1H, br), 6.87 (2H, d, J =

8.6 Hz), 7.00 (4H, br), 7.25 (2H, d, J = 8.6 Hz).

[0266]

Reference Example 221

3-(Methoxyphenyl)-N-(2,2,6,7-tetramethyl-3-(4-

5 methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)-propionamide

Using 2,2,6,7-tetramethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained Reference Example 144 and 3-(methoxyphenyl)propionic acid, the title compound was obtained in the same manner as in Reference Example 215.

10 Yield 64%. Melting point: 149 - 150°C. (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.94 (3H, s), 1.55 (3H, s), 1.98 (3H, s), 2.15 (3H, s), 2.32 (3H, s), 2.58 (2H, d, J = 7.5 Hz), 2.94 (2H, d, J = 7.5 Hz), 3.73 (3H, s), 4.28 (1H, s), 6.63-6.98
15 (6H, m), 7.03-7.18 (4H, m).

[0267]

Reference Example 222

N-(2,2,6,7-Tetramethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

20 Using N-(2,2,6,7-tetramethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran)-5-amine obtained Reference Example 144 and tert-butylacetyl chloride, the title compound was obtained in the same manner as in Reference Example 63 (Yield 88%). Amorphous powder.

25 ¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.08 (9H, s), 1.54 (3H, s),

2.14 (3H, s), 2.17 (5H, s), 2.32 (3H, s), 4.28 (1H, s), 6.75 (1H, brs), 6.90 (1H, s), 6.96 (2H, d, $J = 7.9$ Hz), 7.08 (2H, d, $J = 7.9$ Hz).

[0268]

5 Reference Example 223

N-(2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)butanamide

Using 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example
10 127 and butyl chloride, the title compound was synthesized in the same manner as in Reference Example 63. Yield 50%. Melting point: 138 - 139°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.74-2.41 (25H, m), 4.10 (1H, s), 6.54 (1H, brs), 7.03 (4H, brs).

15 [0269]

Reference Example 224

N-(2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl)pentanamide

Using 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example
20 127 and pentanoyl chloride, the title compound was synthesized in the same manner as in Reference Example 63. Yield 62%. Melting point: 156 - 157°C (ethyl acetate - hexane).

25 $^1\text{H-NMR}$ (CDCl_3) δ : 0.78-2.43 (27H, m), 4.10 (1H, s), 6.55

(1H, brs), 7.04 (4H, brs).

[0270]

Reference Example 225

N-(2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-
5 benzofuran-5-yl)hexanamide

Using 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 127 and hexanoyl chloride, the title compound was synthesized in the same manner as in Reference Example 63.

10 Yield 52%. Melting point: 96 - 97°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.77-2.41 (29H, m), 4.10 (1H, s), 6.55 (1H, brs), 7.03 (4H, brs).

[0271]

15 Reference Example 226

N-(3-(4-Fluorophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-fluorophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 20 128 and tert-butylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63. Yield: 60%. Melting point: 194 - 195°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.12 (9H, s), 1.49 (3H, s),
25 1.77 (3H, s), 2.15 (6H, s), 2.25 (2H, s), 4.11 (1H, s),

6.40-7.20 (5H, m).

[0272]

Reference Example 227

3,3-Dimethyl-N-(2,2,4,6,7-pentamethyl-3-phenyl-2,3-dihydro-
5 1-benzofuran-5-yl)butanamide

Using 2,2,4,6,7-pentamethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 126 and tert-butylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63.
10 Yield: 55%. Melting point: 214 - 215°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.92-1.20 (12H, m), 1.50 (3H, s), 1.77 (3H, s), 2.16 (6H, s), 2.25 (2H, s), 4.13 (1H, s), 6.40-7.38 (6H, m).

15 [0273]

Reference Example 228

N-(3-(4-Bromophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-bromophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 129 and tert-butylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63.
20 Yield: 65%. Melting point: 201 - 202°C (ethyl acetate - hexane).

25 ¹H-NMR (CDCl₃) δ: 0.92-1.18 (12H, m), 1.49 (3H, s), 1.76

(3H, s), 2.15 (6H, s), 2.25 (2H, s), 4.09 (1H, s), 6.51-7.44 (5H, m).

[0274]

Reference Example 229

5 N-(3-(4-tert-Butylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of 3-(4-tert-butylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-ylamine hydrochloride obtained in Reference Example 79 (400 mg, 10 1.16 mmol) and tert-butylacetyl chloride (0.17 mL, 1.22 mmol) in dichloromethane (10 mL) was added triethylamine (0.35 mL, 2.50 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction solution, the organic layer was 15 separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 1 N hydrochloric acid and an aqueous saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. 20 The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 8 : 1) to obtain 110 mg (yield: 41%) of the title compound. Amorphous substance.

¹H-NMR (CDCl₃) δ: 0.99 (3H, s), 1.06 (9H, s), 1.12 (9H, s), 25 1.49 (3H, s), 1.78 (3H, s), 2.16 (6H, s), 2.25 (2H, s),

4.10 (1H, s), 6.50 (1H, br s), 6.70-7.24 (4H, m).

[0275]

Reference Example 230

N-(3-(4-Isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-
5 benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-amine hydrochloride obtained in Reference Example 77, the title compound was synthesized in the same manner as in Reference Example 229. Yield: 38%.

10 Melting point: 172 - 173°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.94 (3H, s), 1.06 (9H, s), 1.23 (6H, d, J = 6.9 Hz), 1.55 (3H, s), 2.15 (3H, s), 2.18 (3H, s), 2.19 (2H, s), 2.87 (1H, septet, J = 6.6 Hz), 4.29 (1H, s), 6.71 (1H, br s), 6.94 (1H, s), 7.00 (2H, d, J = 7.8 Hz), 7.13
15 (2H, d, J = 7.8 Hz).

[0276]

Reference Example 231

N-(3-(4-Isopropylphenyl)-2,2,4,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

20 Using 3-(4-isopropylphenyl)-2,2,4,7-tetramethyl-2,3-dihydro-1-benzofuran-5-amine hydrochloride obtained in Reference Example 78, the title compound was synthesized in the same manner as in Reference Example 229. Yield: 23%.
Melting point: 118 - 119°C (ethyl acetate - hexane).

25 ¹H-NMR (CDCl₃) δ: 1.01 (3H, s), 1.10 (9H, s), 1.21 (6H, d,

J = 6.9 Hz), 1.48 (3H, s), 1.78 (3H, s), 2.19 (2H, s), 2.21 (3H, s), 2.85 (1H, septet, J = 6.9 Hz), 4.08 (1H, s), 6.52-7.24 (6H, m).

[0277]

5 Reference Example 232

N-(3-(4-Isopropylphenyl)-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example
10 81 and tert-butylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63.
Yield: 52%. Amorphous substance.

¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.11 (9H, s), 1.21 (6H, d, J = 6.9 Hz), 1.49 (3H, s), 1.79 (3H, s), 2.21 (3H, s), 2.23
15 (2H, s), 2.84 (1H, septet, J = 6.9 Hz), 4.08 (1H, s), 6.53 (1H, br s), 6.56 (1H, s), 6.70-7.10 (4H, m).

[0278]

Reference Example 233

N-(3-(4-Isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-
20 benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 89 and tert-butylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63.
25 Yield: 52%. Melting point: 126 - 127°C (ethyl acetate -

hexane).

¹H-NMR (CDCl₃) δ: 0.96 (3H, s), 1.07 (9H, s), 1.24 (6H, d, J = 6.6 Hz), 1.56 (3H, s), 2.12 (2H, s), 2.88 (1H, septet, J = 6.6 Hz), 4.29 (1H, s), 6.75 (1H, d, J = 8.1 Hz), 6.91
5 (1H, br s), 6.99 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 8.1 Hz), 7.16-7.25 (2H, m).

[0279]

Reference Example 234

N-(3-(4-Isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-
10 benzofuran-5-yl)butanamide

Using 3-(4-isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 89 and butyryl chloride, the title compound was synthesized in the same manner as in Reference Example 63. Yield: 27%.

15 Amorphous substance.

¹H-NMR (CDCl₃) δ: 0.97 (3H, s), 0.98 (3H, t, J = 7.2 Hz), 1.24 (6H, d, J = 6.9 Hz), 1.56 (3H, s), 1.60-1.80 (2H, m), 2.26 (2H, t, J = 7.5 Hz), 2.88 (1H, septet, J = 6.9 Hz), 4.29 (1H, s), 6.75 (1H, d, J = 9.3 Hz), 6.90-7.05 (3H, m),
20 7.13 (2H, d, J = 8.1 Hz), 7.17-7.22 (2H, m).

[0280]

Reference Example 235

N-(3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)butanamide

25 Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-

dihydro-1-benzofuran-5-amine obtained in Reference Example 125 and butyryl chloride, the title compound was synthesized in the same manner as in Reference Example 63. Yield: 59%. Melting point: 120 - 122°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.78-1.10 (6H, m), 1.21 (6H, d, J = 6.9 Hz), 1.60-1.90 (8H, m), 2.10-2.40 (8H, m), 2.84 (1H, septet, J = 6.9 Hz), 4.10 (1H, s), 6.50-7.20 (5H, m).

[0281]

10 Reference Example 236

N-(3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)pentanamide

Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 125 and pentanoyl chloride, the title compound was synthesized in the same manner as in Reference Example 63. Yield: 44%. Melting point: 106 - 107°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.70-1.90 (22H, m), 2.05-2.41 (8H, m), 2.84 (1H, septet, J = 6.6 Hz), 4.10 (1H, s), 6.42-7.18 (5H, m).

[0282]

Reference Example 237

N-(3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 125 and tert-butylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63.

5 Yield: 41%. Amorphous substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.90-1.20 (12H, m), 1.21 (6H, d, $J = 7.2$ Hz), 1.48 (3H, s), 1.78 (3H, s), 2.15-2.27 (8H, m), 2.84 (1H, septet, $J = 7.2$ Hz), 4.09 (1H, s), 6.40-7.10 (5H, m).

[0283]

10 Reference Example 238

N-(3-(4-Isopropylphenyl)-2,4,6,7-tetramethyl-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-2,4,6,7-tetramethyl-1-benzofuran-5-amine hydrochloride obtained in Reference

15 Example 131, the title compound was synthesized in the same manner as in Reference Example 229. Yield: 24%. Melting point: 253 - 254°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.14 (9H, s), 1.30 (6H, d, $J = 6.9$ Hz), 1.97 (3H, s), 2.25 (3H, s), 2.30 (5H, s), 2.43 (3H, s),
20 2.96 (1H, septet, $J = 6.9$ Hz), 6.62 (1H, br s), 7.23 (4H, s).

[0284]

Reference Example 239

N-(3-(4-Isopropylphenyl)-2,2,4,5,7-pentamethyl-2,3-dihydro-
25 1-benzofuran-6-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-2,2,4,5,7-pentamethyl-2,3-dihydro-1-benzofuran-6-amine obtained in Reference Example 80 and tert-butylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63.

5 Yield: 50%. Melting point: 128 - 129°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.02 (3H, s), 1.17 (9H, s), 1.21 (6H, d, J = 6.9 Hz), 1.48 (3H, s), 1.83 (3H, s), 2.04 (3H, s), 2.12 (3H, s), 2.31 (2H, s), 2.84 (1H, septet, J = 7.2 Hz), 4.10
10 (1H, s), 6.50-7.18 (5H, m).

[0285]

Reference Example 240

N-(3-Benzyl-2,2,4,5,7-pentamethyl-2,3-dihydro-1-benzofuran-6-yl)-3,3-dimethylbutanamide

15 Using 3-benzyl-2,2,4,5,7-pentamethyl-2,3-dihydro-1-benzofuran-6-amine obtained in Reference Example 82 and tert-butylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63. Yield: 38%. Melting point: 209 - 210°C (ethyl acetate -
20 hexane).

¹H-NMR (CDCl₃) δ: 1.15 (9H, s), 1.26 (3H, s), 1.40 (3H, s), 1.80 (3H, s), 2.01 (3H, s), 2.07 (3H, s), 2.29 (2H, s), 2.75 (1H, dd, J = 14.7, 6.0 Hz), 2.89 (1H, dd, J = 14.7, 8.4 Hz), 3.29 (1H, dd, J = 8.4, 6.0 Hz), 6.60 (1H, br s),
25 7.10-7.30 (5H, m).

[0286]

Reference Example 241

N-(3-(4-Isopropylphenyl)-2,2,5-trimethyl-2,3-dihydro-1-benzofuran-7-yl)-3,3-dimethylbutanamide

5 Using 3-(4-isopropylphenyl)-2,2,5-trimethyl-2,3-dihydro-1-benzofuran-7-amine obtained in Reference Example 99, the title compound was synthesized in the same manner as in Reference Example 63. Yield: 51%. Melting point: 64 - 68°C (hexane).

10 ¹H-NMR (CDCl₃) δ: 0.95 (3H, s), 1.12 (9H, s), 1.24 (6H, d, J = 6.9 Hz), 1.57 (3H, s), 2.25 (3H, s), 2.27 (2H, s), 2.89 (1H, septet, J = 6.9 Hz), 4.30 (1H, s), 6.59 (1H, s), 6.99 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 8.1 Hz), 7.17 (1H, br s), 7.98 (1H, s).

15 [0287]

Reference Example 242

(+)-(3R)-3-(4-Isopropylphenyl)-3,5-dimethyl-2,3-dihydro-1-benzofuran-5-amine

20 A suspension of 3-(4-isopropylphenyl)-3,5-dimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 32 (22.5 g, 80 mmol) and (2S, 3S)-(4'-methyl)-tartranilic acid (19.14 g, 80 mmol) in ethanol (480 mL) was heated at 85°C for dissolution. The solution was cooled to 0°C over 2 hours, and the precipitated crystals were taken.

25 The crystals were washed with cold ethanol, and then were

dried under reduced pressure. The obtained crystals were suspended in a 2 N aqueous sodium hydroxide solution (400 mL), which was extracted with diethyl ether. The extract was washed with a saturated sodium hydrogen carbonate solution and a saturated brine, and then was dried over sodium sulfate. The solvent was distilled off under reduced pressure to obtain 9.44 g (yield 34%) of the title compound as an oily matter. The obtained oily matter was, if necessary, crystallized with cold hexane. Melting point: 53 - 55°C. $[\alpha]_D^{20} = +64.0^\circ$ (c = 0.44, chloroform). $^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (6H, d, J = 6.9 Hz), 1.85 (3H, s), 2.18 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.52 (2H, br), 4.34 (1H, dd, J = 4.7, 8.8 Hz), 4.50 (1H, dd, J = 4.7, 8.8 Hz), 4.76 (1H, t, J = 8.8 Hz), 6.56 (1H, s), 7.04 (2H, d, J = 8.0 Hz), 7.12 (2H, d, J = 8.0 Hz).

[0288]

Reference Example 243

N-(3-(4-Isopropylphenyl)-5-methoxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-7-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-5-methoxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-7-amine obtained in Reference Example 100 and tert-butylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63. Yield: 67%. Melting point: 140 - 141°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.96 (3H, s), 1.14 (9H, s), 1.22 (6H, d, J = 6.9 Hz), 1.47 (3H, s), 1.83 (3H, s), 2.20 (3H, s), 2.28 (2H, s), 2.85 (1H, septet, J = 6.9 Hz), 3.64 (3H, s), 4.10 (1H, s), 6.40-7.18 (5H, m).

5 [0289]

Reference Example 244

N-(3-(4-Isopropylphenyl)-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-N,3,3-trimethylbutanamide

To a solution of N-(3-(4-isopropylphenyl)-2,2-
10 dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-
dimethylbutanamide (110 mg, 290 μmol) obtained in Reference
Example 233 in DMF (3 mL) was added sodium hydride (a 60%
dispersion in liquid paraffin, 12.8 mg, 319 μmol) at 0°C
and the mixture was stirred at room temperature for 30
15 minutes. Methyl iodide (8.0 g, 319 μmol) was added to the
reaction solution and the mixture was stirred at room
temperature for 30 minutes. Water was added to the
reaction solution and the product was extracted with
diisopropyl ether. The combined extracts were washed with
20 water, dried over magnesium sulfate, and concentrated under
reduced pressure. The obtained residue was purified by
silica gel column chromatography (hexane : ethyl acetate =
4 : 1) to obtain 47 mg (yield: 41%) of the title compound.
Melting point: 78 - 79°C (ethyl acetate - hexane).

25 ¹H-NMR (CDCl₃) δ: 0.93 (9H, s), 1.00 (3H, s), 1.24 (6H, d,

$J = 7.0$ Hz), 1.62 (3H, s), 1.94-2.10 (2H, m), 2.90 (1H, septet, $J = 7.0$ Hz), 3.19 (3H, s), 4.36 (1H, s), 6.77-6.92 (3H, m), 6.98 (2H, d, $J = 8.0$ Hz), 7.16 (2H, d, $J = 8.0$ Hz).

[0290]

5 Reference Example 245

N-(3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3-(4-morpholinyl)propionamide hydrochloride

To a solution of 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine (350 mg, 1.08 mmol) obtained in Reference Example 125 and 3-chloropropionyl chloride (0.39 mL, 3.72 mmol) in dichloromethane (15 mL) was added triethylamine (0.18 mL, 1.30 mmol) at room temperature and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction solution, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 1 N hydrochloric acid and an aqueous saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to obtain a crude product of N-(3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-3-chloropropionamide. A mixture of the compound, morpholine and potassium carbonate in ethanol was refluxed with heating for 16 hours. The

mixture was poured into water and the product was extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to obtain a free base of the title compound. The compound was crystallized from 4 N hydrochloric acid - ethyl acetate to obtain 230 mg (yield: 42%) of the title compound. Melting point: 158 - 161°C (methanol - diethyl ether).

¹H-NMR (DMSO-d₆) δ: 0.94 (3H, s), 1.17 (6H, d, J = 6.9 Hz), 1.43 (3H, s), 1.66 (3H, s), 2.02 (3H, s), 2.09 (3H, s), 2.77-2.98 (3H, m), 3.08-3.18 (2H, m), 3.25-3.47 (4H, m), 3.80 (2H, t, J = 12.0 Hz), 3.94 (2H, d, J = 11.4 Hz), 4.18 (1H, s), 4.42 (1H, br s), 6.60-7.20 (4H, m), 9.35 (1H, s).

[0291]

Reference Example 246

N-(3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-4-methoxyphenylacetamide

Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 125 and 4-methoxyphenylacetyl chloride, the title compound was synthesized in the same manner as in Reference Example 63. Yield 74%. Melting point: 171 - 173°C (methanol).

¹H-NMR (CDCl₃) δ: 0.98 (3H, s), 1.20 (6H, d, J = 6.6 Hz),

1.46 (3H, s), 1.64 (3H, s), 2.03 (3H, s), 2.12 (3H, s),
2.84 (1H, septet, J = 6.6 Hz), 3.68 (2H, s), 3.80 (3H, s),
4.06 (1H, s), 6.45 (1H, br), 6.6-6.9 (2H, m), 6.89 (2H, d,
J = 8.6 Hz), 7.05 (2H, d, J = 8.0 Hz), 7.26 (d, 2H, J = 8.6
5 Hz).

[0292]

Reference Example 247

N-(3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-
1-benzofuran-5-yl)-3-(4-methoxyphenyl)propionamide

10 Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-
dihydro-1-benzofuran-5-amine obtained in Reference Example
125 and 4-methoxyphenylpropionyl chloride, the title
compound was synthesized in the same manner as in Reference
Example 63. Yield 72%. Melting point: 188 - 191°C. (ethyl
15 acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.99-1.01 (3H, m), 1.19-1.26 (6H, m),
1.48 (3H, s), 1.64-1.68 (3H, m), 1.99 (3H, s), 2.05-2.13
(5H, m), 2.65-3.04 (3H, m), 3.72-3.77 (3H, m), 4.08 (1H, s),
6.47-7.19 (9H, m).

20 [0293]

Reference Example 248

N-(3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-
1-benzofuran-5-yl)-N-(2-(4-methoxyphenyl)ethyl)acetamide

To a suspension of aluminum chloride (1.23 g, 9.25
25 mmol) in THF (40 mL) was slowly added lithium aluminium

hydride (354 mg, 9.31 mmol) with ice-cooling, and the mixture was stirred at the same temperature for 10 minutes. To this mixture was added N-(3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)-4-methoxyphenylacetamide obtained in Reference Example 246 (536 mg, 1.14 mmol), and the mixture was heated under reflux for 3 hours. The reaction mixture was added to ice-water, and the mixture was neutralized with a 8 N aqueous sodium hydroxide solution. Thereafter, the product was twice extracted with ethyl acetate, and the combined organic layer was washed with water, dried over magnesium sulfate, filtered and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain 3-(4-isopropylphenyl)-N-(2-(4-methoxyphenyl)ethyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine. This compound (537.9 mg, 1.18 mmol) was added to a suspension of sodium hydride (a 60% paraffin dispersion, 232.1 mg, 5.80 mmol) in DMF (25 mL) at 60°C, and the mixture was stirred for 20 minutes. Acetyl chloride (0.5 mL, 7.03 mmol) was added thereto, and the mixture was stirred at the same temperature for 1 hour. The reaction mixture was cooled to room temperature, and a saturated sodium hydrogen carbonate solution was added to the mixture, which was twice extracted with ethyl acetate. The extract

was washed with water, dried over magnesium sulfate, filtered and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain the rotational isomer of the object compound (R_f = 0.38; hexane : ethyl acetate = 3 : 1) (yield 43%). Melting point: 134 - 136°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.03 (3H, s), 1.22 (6H, d, J = 7.0 Hz), 1.54 (3H, s), 1.66 (3H, s), 1.72 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 2.77-2.89 (3H, m), 3.59-3.70 (2H, m), 3.77 (3H, s), 4.11 (1H, s), 6.77-7.13 (8H, m).

[0294]

Reference Example 249

N -(3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)- N -(2-(4-methoxyphenyl)ethyl)acetamide

The residue, as operated in the same manner as in Reference Example 248, was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain the rotational isomer of the object compound (R_f = 0.25; hexane : ethyl acetate = 3 : 1) (yield 34%). Amorphous matter.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.03 (3H, s), 1.23 (6H, d, J = 6.8 Hz), 1.53 (3H, s), 1.73 (3H, s), 1.75 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 2.67-2.75 (2H, m), 2.80-2.94 (1H, septet, J = 6.8 Hz), 3.57-3.74 (2H, m), 3.77 (3H, s), 4.14 (1H, s),

6.77-7.13 (8H, m).

[0295]

Reference Example 250

1-(4-Isopropylphenyl)-2-(3,5-dimethylphenoxy)ethanone

5 To a solution of cumene (27.8 mL, 200 mmol) and
aluminum chloride (32.0 g, 240 mmol) in dichloromethane
(300 mL) was added bromoacetyl bromide (19.1 mL, 220 mmol)
at -10°C, and the mixture was stirred at the same
temperature for 2 hours. The reaction solution was poured
10 into ice-cold water, and an organic layer was separated.
The organic layer was washed with a saturated sodium
hydrogen carbonate solution and a saturated brine, and then
was dried over sodium sulfate. The solvent was distilled
off under reduced pressure, and the residue was purified by
15 silica gel column chromatography (ethyl acetate : hexane =
1 : 9) to obtain 2-bromo-1-(4-isopropylphenyl)ethanone of
oily matter. The obtained oily matter was added to a
solution of 3,5-dimethylphenol (29.3 g, 240 mmol) and
potassium carbonate (33.2 g, 240 mmol) in acetone (500 mL),
20 and the mixture then was stirred under heat and reflux for
12 hours. The reaction solution was ice-cooled and poured
into cold water, which was extracted with diethyl ether.
The extract was washed with a saturated brine, and then was
dried over sodium sulfate. Then, the solvent was distilled
25 off under the reduced pressure, and the residue was

purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 4). The obtained oily matter was crystallized with hexane to obtain 39.4 g (yield 75%) of the title compound. Melting point: 68 - 69°C.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.28 (6H, d, $J = 6.9$ Hz), 2.27 (3H, s), 2.28 (3H, s), 2.98 (1H, septet, $J = 6.9$ Hz), 5.22 (2H, s), 6.57 (2H, s), 6.63 (1H, s), 7.35 (2H, d, $J = 8.4$ Hz), 7.95 (2H, d, $J = 8.4$ Hz).

[0296]

10 Reference Example 251

3-(4-Isopropylphenyl)-4,6-dimethylbenzofuran

A solution of 1-(4-isopropylphenyl)-2-(3,5-dimethylphenoxy)ethanone obtained in Reference Example 250 (38.1 g, 135 mmol) and Montmorillonite KSF (57.2 g) in
15 toluene (400 mL) was heated at 95°C, and was reacted for 16 hours. The reaction solution was cooled to room temperature, and then Montmorillonite KSF was filtered off. The solution was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 9), and the
20 solvent was distilled off under reduced pressure to obtain 35.6 g (yield 100%) of the title compound as an oily matter. The oily matter was, if necessary, crystallized with methanol. Melting point: 44 - 45°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.30 (6H, d, $J = 6.9$ Hz), 2.30 (3H, s),
25 2.43 (3H, s), 2.96 (1H, septet, $J = 6.9$ Hz), 6.83 (1H, s),

7.18 (1H, s), 7.25 (2H, d, J = 8.6 Hz), 7.45 (2H, d, J = 8.6 Hz).

[0297]

Reference Example 252

5 3-(4-Isopropylphenyl)-3,5-dimethyl-2,3-dihydro-1-benzofuran
3-(4-Isopropylphenyl)-3,5-dimethyl-2,3-dihydro-1-
benzofuran (36.5 g, 135 mmol) obtained in Reference Example
251 and 10% - palladium carbon (50% hydrous, 3.7 g) were
suspended in ethanol (400 mL), and reductive reaction was
10 performed under hydrogen atmosphere of 5 atmospheric
pressure at 60°C for 6 hours. The reaction solution was
cooled to room temperature, the catalyst was filtered off,
and the solution was concentrated under reduced pressure.
The obtained oily matter was crystallized with methanol to
15 obtain 27.5 g (yield 77%) of the title compound. Melting
point: 48 - 50°C.

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, J = 6.9 Hz), 1.92 (3H, s),
2.29 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 4.35-4.53 (2H,
m), 4.83 (1H, t, J = 8.1 Hz), 6.47 (1H, s), 6.56 (1H, s),
20 7.04 (2H, d, J = 8.2 Hz), 7.13 (2H, d, J = 8.2 Hz).

[0298]

Example 1

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-
benzofuran-5-yl)-3,3-dimethylbutanamide

25 To a solution of 3-(4-isopropylphenyl)-4,6,7-

trimethyl-2,3-dihydro-1-benzofuran-5-amine (430 mg, 1.46 mmol) obtained in Reference Example 30 and tert-butylacetyl chloride (0.22 mL, 1.53 mmol) in dichloromethane (10 mL) was added triethylamine (0.22 mL, 1.61 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 1 hour. Water was added to the reaction solution, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 1 N hydrochloric acid and an aqueous saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 8 : 1) to obtain 400 mg (yield: 70%) of the title compound. Melting point: 171 - 173°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.12 (9H, s), 1.21 (6H, d, $J = 6.9$ Hz), 1.81 (3H, s), 2.15 (3H, s), 2.17 (3H, s), 2.25 (2H, s), 2.86 (1H, septet, $J = 6.9$ Hz), 4.41 (1H, dd, $J = 8.7, 4.8$ Hz), 4.52 (1H, dd, $J = 8.7, 4.8$ Hz), 4.82 (1H, t, $J = 8.7$ Hz), 6.49 (1H, br s), 7.04 (2H, d, $J = 8.1$ Hz), 7.12 (2H, d, $J = 8.4$ Hz).

[0299]

Example 2

N-(3-(4-Isopropylphenyl)-6,7-dimethyl-2,3-dihydro-1-

benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-6,7-dimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 31, the title compound was synthesized in the same manner as in

5 Example 1. Yield: 54%. Melting point: 177 - 178°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.09 (9H, s), 1.24 (6H, d, J = 7.2 Hz), 2.13 (3H, s), 2.18 (2H, s), 2.20 (3H, s), 2.87 (1H, septet, J = 7.2 Hz), 4.28 (1H, dd, J = 9.0, 7.5 Hz), 4.56-4.63 (1H, 10 m), 4.84 (1H, t, J = 9.0 Hz), 6.69 (1H, br s), 6.94 (1H, s), 7.11 (2H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.4 Hz).

[0300]

Example 3

15 N-(3-(4-Isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 32, the title compound was synthesized in the same manner as in

20 Example 1. Yield: 67%. Melting point: 130 - 131°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.11 (9H, s), 1.21 (6H, d, J = 6.9 Hz), 1.85 (3H, s), 2.21 (3H, s), 2.23 (2H, s), 2.85 (1H, septet, J = 6.9 Hz), 4.40 (1H, dd, J = 8.4, 4.8 Hz), 4.49 (1H, dd, J = 9.0, 4.8 Hz), 4.77-4.85 (1H, m), 6.48 (1H, br s), 6.62 25 (1H, s), 7.03 (2H, d, J = 8.1 Hz), 7.11 (2H, d, J = 8.1 Hz).

[0301]

Example 4

N-(3-(4-Isopropylphenyl)-2,3-dihydro-1-benzofuran-5-yl)-
3,3-dimethylbutanamide

5 Using 3-(4-isopropylphenyl)-2,3-dihydro-1-benzofuran-
5-amine obtained in Reference Example 33, the title
compound was synthesized in the same manner as in Example 1.
Yield: 71%. Melting point: 119 - 120°C (ethyl acetate -
hexane).

10 ¹H-NMR (CDCl₃) δ: 1.06 (9H, s), 1.23 (6H, d, J = 6.9 Hz),
2.13 (2H, s), 2.88 (1H, septet, J = 6.9 Hz), 4.40 (1H, dd,
J = 9.0, 7.5 Hz), 4.56-4.64 (1H, m), 4.87 (1H, t, J = 9.0
Hz), 6.79 (1H, d, J = 8.7 Hz), 6.89 (1H, br s), 7.08-7.23
(6H, m)

15 [0302]

Example 5

N-(3-(4-Isopropylphenyl)-3,4,6,7-tetramethyl-2,3-dihydro-1-
benzofuran-5-yl)-3,3-dimethylbutanamide

20 Using 3-(4-isopropylphenyl)-3,4,6,7-tetramethyl-2,3-
dihydro-1-benzofuran-5-amine obtained in Reference Example
34, the title compound was synthesized in the same manner
as in Example 1. Yield: 37%. Melting point: 194 - 195°C
(ethyl acetate - hexane).

25 ¹H-NMR (CDCl₃) δ: 1.12 (9H, s), 1.23 (6H, d, J = 6.9 Hz),
1.72 (3H, s), 1.74 (3H, s), 2.15 (3H, s), 2.17 (3H, s),

2.24 (2H, s), 2.87 (1H, septet, $J = 6.9$ Hz), 4.37 (1H, d, $J = 8.4$ Hz), 4.42 (1H, d, $J = 8.4$ Hz), 6.48 (1H, br s), 7.13 (2H, d, $J = 8.4$ Hz), 7.21 (2H, d, $J = 8.4$ Hz).

[0303]

5 Example 6

N-(3-(4-Isopropylphenyl)-3,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using 3-(4-isopropylphenyl)-3,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example
10 35, the title compound was synthesized in the same manner as in Example 1. Yield: 59%. Melting point: 132 - 133°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (9H, s), 1.22 (6H, d, $J = 6.9$ Hz), 1.71 (3H, s), 2.14 (3H, s), 2.19 (3H, s), 2.20 (2H, s),
15 2.86 (1H, septet, $J = 6.9$ Hz), 4.40 (1H, d, $J = 8.7$ Hz), 4.57 (1H, d, $J = 8.7$ Hz), 6.72 (1H, br s), 6.97 (1H, s), 7.13 (2H, d, $J = 8.4$ Hz), 7.20 (2H, d, $J = 8.4$ Hz).

[0304]

Example 7

20 (+)-N-((3R)-3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in
Example 1 was separated using high performance liquid
25 chromatography (apparatus: GIGAPREP SK-1 manufactured by

Shiseido Co., Ltd., Column: CHIRALCEL OD (50 (i, d) × 500 mm) manufactured by Daicel Chemical Industries, Ltd.), Mobile phase: hexane : ethanol = 95 : 5, Flow rate: 60 mL/min, Column temperature: 35°C, Sample injection amount: 30 mg/times, Detect: UV 220 nm), and a shorter retention time was obtained as the title compound. Recovery: 44%. Melting point: 186 - 187°C (ethyl acetate - hexane). $[\alpha]_D^{20} = +64.0^\circ$ (c = 0.44, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.12 (9H, s), 1.21 (6H, d, J = 6.9 Hz), 1.84 (3H, s), 2.14 (3H, s), 2.17 (3H, s), 2.25 (2H, s), 2.85 (1H, septet, J = 6.9 Hz), 4.40 (1H, dd, J = 8.7, 4.8 Hz), 4.51 (1H, dd, J = 9.3, 4.8 Hz), 4.81 (1H, t, J = 9.0 Hz), 6.47 (1H, br s), 7.03 (2H, d, J = 8.4 Hz), 7.11 (2H, d, J = 8.4 Hz).

[0305]

Example 8

(-)-N-((3S)-3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in

Example 1 was separated using high performance liquid chromatography (apparatus: GIGAPREP SK-1 manufactured by Shiseido Co., Ltd., Column: CHIRALCEL OD (50 (i, d) × 500 mm) manufactured by Daicel Chemical Industries, Ltd.),

Mobile phase: hexane : ethanol = 95 : 5, Flow rate: 60

mL/min, Column temperature: 35°C, Sample injection amount: 30 mg/times, Detect: UV 220 nm), and a longer retention time was obtained as the title compound. Recovery: 42%.

Melting point: 185 - 186°C (ethyl acetate - hexane). $[\alpha]_D^{20}$
 5 = -61.2° (c = 0.42, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.12 (9H, s), 1.21 (6H, d, J = 6.9 Hz),
 1.84 (3H, s), 2.14 (3H, s), 2.17 (3H, s), 2.24 (2H, s),
 2.85 (1H, septet, J = 6.9 Hz), 4.40 (1H, dd, J = 8.7, 4.8
 10 Hz), 4.51 (1H, dd, J = 9.0, 4.8 Hz), 4.81 (1H, t, J = 8.7
 Hz), 6.49 (1H, br s), 7.03 (2H, d, J = 8.1 Hz), 7.10 (2H, d,
 J = 8.1 Hz).

[0306]

Example 9

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-
 15 benzofuran-5-yl)propionamide

Using 3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-
 dihydro-1-benzofuran-5-amine obtained in Reference Example
 30 and propionyl chloride, the title compound was
 synthesized in the same manner as in Example 1. Yield: 74%.
 20 Melting point: 164 - 165°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.00-1.37 (9H, m), 1.82 (3H, s), 2.09-
 2.45 (8H, m), 2.85 (1H, septet, J = 6.9 Hz), 4.37-4.60 (2H,
 m), 4.77-4.89 (1H, m), 6.54 (1H, br s), 6.99-7.19 (4H, m)

[0307]

25 Example 10

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)butanamide

Using 3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 30 and butyryl chloride, the title compound was synthesized in the same manner as in Example 1. Yield: 80%. Melting point: 177 - 178°C (THF - diisopropyl ether).

¹H-NMR (CDCl₃) δ: 1.02 (3H, t, J = 7.5 Hz), 1.22 (6H, d, J = 6.9 Hz), 1.71-1.87 (5H, m), 2.13 (3H, s), 2.18 (3H, s), 2.35 (2H, t, J = 7.5 Hz), 2.86 (1H, septet, J = 6.9 Hz), 4.42 (1H, dd, J = 9.0, 4.5 Hz), 4.53 (1H, dd, J = 9.0, 4.5 Hz), 4.83 (1H, t, J = 9.0 Hz), 6.54 (1H, br s), 6.99-7.06 (2H, m), 7.11-7.15 (2H, m).

[0308]

Example 11

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)pentanamide

Using 3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 30 and pentanoyl chloride, the title compound was synthesized in the same manner as in Example 1. Yield: 72%. Melting point: 128 - 129°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.72-1.00 (3H, m), 1.21 (6H, d, J = 6.9 Hz), 1.36-1.90 (7H, m), 2.11-2.42 (8H, m), 2.85 (1H, septet, J = 6.9 Hz), 4.37-4.59 (2H, m), 4.77-4.89 (1H, m), 6.53 (1H,

br s), 6.99-7.17 (4H, m).

[0309]

Example 12

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-(4-methoxyphenyl)acetamide

Using 3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 30 and (4-methoxyphenyl)acetyl chloride, the title compound was synthesized in the same manner as in Example 1. Yield: 62%. Melting point: 166 - 167°C (Methanol).

¹H-NMR (CDCl₃) δ: 1.20 (6H, d, J = 6.9 Hz), 1.72 (3H, s), 2.02 (3H, s), 2.14 (3H, s), 2.83 (1H, septet, J = 6.9 Hz), 3.69 (2H, s), 3.80 (3H, s), 4.39 (1H, dd, J = 9.0, 4.5 Hz), 4.48 (1H, dd, J = 9.0, 4.5 Hz), 4.80 (1H, t, J = 9.0 Hz), 6.46 (1H, br s), 6.90 (2H, d, J = 8.4 Hz), 7.01 (2H, d, J = 8.4 Hz), 7.13 (2H, d, J = 8.4 Hz), 7.26 (2H, d, J = 8.4 Hz).

[0310]

Example 13

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-3-(4-methoxyphenyl)propionamide

Using 3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 30 and 3-(4-methoxyphenyl)propionyl chloride, the title compound was synthesized in the same manner as in Example 1. Yield: 83%. Melting point: 119 - 120°C (ethyl acetate -

hexane).

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, J = 7.2 Hz), 1.66-1.75 (3H, m), 1.97-2.20 (6H, m), 2.61-3.02 (5H, m), 3.71-3.78 (3H, m), 4.35-4.56 (2H, m), 4.77-4.85 (1H, m), 6.45 (1H, br s),
5 6.62-7.20 (8H, m).

[0311]

Example 14

N-(tert-Butyl)-N'-(3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)urea

10 To a solution of 3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine (300 mg, 1.02 mmol) obtained in Reference Example 30 in dichloromethane (5 mL) was added tert-butyl isocyanate (0.14 mL, 1.22 mmol) and the resulting mixture was refluxed for 20 hours. The
15 reaction solution was added to water and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The
20 residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and recrystallized from THF-hexane to obtain 283 mg (yield: 70%) of the title compound. Melting point: 201 - 202°C.

¹H-NMR (CDCl₃) δ: 1.10-1.40 (15H, m), 1.87 (3H, s), 2.19 (6H, s), 2.86 (1H, septet, J = 6.9 Hz), 4.00 (1H, br s),
25 4.45 (1H, dd, J = 8.7, 4.5 Hz), 4.55 (1H, dd, J = 8.7, 4.5

Hz), 4.86 (1H, t, $J = 8.7$ Hz), 5.31 (1H, br s), 7.00 (2H, d, $J = 8.0$ Hz), 7.12 (2H, d, $J = 8.0$ Hz).

[0312]

Example 15

5 Ethyl (3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)oxamate

Using 3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine obtained in Reference Example 30 and ethyloxalyl chloride, the title compound was
10 synthesized in the same manner as in Example 1. Yield: 76%.
Melting point: 83 - 84°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (6H, d, $J = 6.9$ Hz), 1.42 (3H, t, $J = 7.2$ Hz), 1.83 (3H, s), 2.13 (3H, s), 2.19 (3H, s), 2.86 (1H, septet, $J = 6.9$ Hz), 4.37-4.46 (3H, m), 4.54 (1H, dd, $J = 9.0, 4.5$ Hz), 4.85 (1H, t, $J = 9.0$ Hz), 7.04 (2H, d, $J = 8.1$ Hz), 7.13 (2H, d, $J = 8.1$ Hz), 8.27 (1H, br s).

[0313]

Example 16

20 N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethyl-2-oxobutanamide

To a solution of ethyl (3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)oxamate (100 mg, 0.25 mmol) obtained in Example 15 in THF (3 ml) was added dropwise at 0°C under an argon atmosphere tert-
25 butylmagnesium chloride (2.0 M THF solution, 0.26 mL, 0.5

mmol) and the mixture was stirred for 30 minutes. After the reaction solution was stirred at room temperature for 1 hour, the reaction solution was added to ice and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) and recrystallized from ethyl acetate - hexane to obtain 29 mg (yield: 28%) of the title compound. Melting point: 142 - 143°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (6H, d, $J = 6.9$ Hz), 1.37 (9H, s), 1.81 (3H, s), 2.10 (3H, s), 2.18 (3H, s), 2.86 (1H, septet, $J = 6.9$ Hz), 4.42 (1H, dd, $J = 9.0, 4.5$ Hz), 4.52 (1H, dd, $J = 9.0, 4.5$ Hz), 4.82 (1H, t, $J = 9.0$ Hz), 7.03 (2H, d, $J = 7.8$ Hz), 7.12 (2H, d, $J = 7.8$ Hz), 8.00 (1H, br s).

[0314]

Example 17

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-oxobutanamide

To a solution of 2-oxobutanoic acid (259 mg, 2.54 mmol) in THF (5 mL) was added dropwise with ice-cooling oxalyl chloride (0.33 mL, 3.80 mmol) and added DMF (three drops), and the mixture was stirred for 30 minutes. The reaction solution was warmed to room temperature and

stirred at the same temperature for 1 hour, and then the solvent was distilled off under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and the product was added dropwise with ice-cooling to a solution of 3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-amine (500 mg, 1.69 mmol) obtained in Reference Example 30 and triethylamine (0.24 mL, 1.69 mmol) in THF (5 mL), and the resulting mixture was stirred for 30 minutes. After the reaction solution was warmed to room temperature, water was added to the reaction solution and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 363 mg (yield: 57%) of the title compound. Yield: 57%. Melting point: 97 - 98°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.15 (3H, t, $J = 7.2$ Hz), 1.22 (6H, d, $J = 6.9$ Hz), 1.79 (3H, s), 2.09 (3H, s), 2.18 (3H, s), 2.86 (1H, septet, $J = 6.9$ Hz), 3.01 (2H, q, $J = 7.2$ Hz), 4.42 (1H, dd, $J = 9.0, 4.5$ Hz), 4.53 (1H, dd, $J = 9.0, 4.5$ Hz), 4.83 (1H, t, $J = 9.0$ Hz), 7.03 (2H, d, $J = 7.8$ Hz), 7.12 (2H, d, $J = 7.8$ Hz), 8.13 (1H, s).

Example 18

2-Hydroxy-N-(3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)butanamide

To a solution of N-(3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-oxobutanamide
5 obtained in Example 17 (237 mg, 0.62 mmol) in methanol (5 mL) was added sodium borohydride (24 mg, 0.62 mmol) at 0°C and the resulting mixture was stirred at room temperature for 30 minutes. Water was added to the reaction solution
10 and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - hexane to obtain 170 mg (yield: 72%) of the
15 title compound. Melting point: 146 - 147°C.

¹H-NMR (CDCl₃) δ: 1.06 (3H, t, J = 7.5 Hz), 1.22 (6H, d, J = 6.9 Hz), 1.70-1.88 (4H, m), 1.88-2.05 (1H, m), 2.12 (3H, s), 2.18 (3H, s), 2.50-2.60 (2H × 0.5, m), 2.86 (1H, septet, J = 6.9 Hz), 4.22-4.28 (2H × 0.5, m), 4.41 (1H, dd, J =
20 9.0, 4.5 Hz), 4.52 (1H, dd, J = 9.0, 4.5 Hz), 4.82 (1H, t, J = 9.0 Hz), 7.03 (2H, d, J = 7.5 Hz), 7.11 (2H, d, J = 7.5 Hz), 7.58 (1H × 0.5, br s), 7.60 (1H × 0.5, br s).

[0316]

Example 19

25 2-Hydroxy-N-(3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-

dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of ethyl (3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)oxamate (500 mg, 1.26 mmol) obtained in Example 15 in THF (10 mL) was added dropwise at 0°C under an argon atmosphere tert-butylmagnesium chloride (2.0 M THF solution, 1.9 mL, 3.78 mmol) and the mixture was stirred for 30 minutes. After the reaction solution was warmed to room temperature and was stirred at the same temperature for 1 hour, the reaction solution was added to ice and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) and recrystallized from ethyl acetate - hexane to obtain 194 mg (yield: 38%) of the title compound as a diastereomer mixture. Melting point: 165 - 166°C.

¹H-NMR (CDCl₃) δ: 1.09 (9H, s), 1.20-1.26 (6H, m), 1.84 (3H, s), 2.14 (3H, s), 2.18 (3H, s), 2.64 (1H × 0.5, d, J = 5.1 Hz), 2.70 (1H × 0.5, d, J = 5.1 Hz), 2.80-2.92 (1H, m), 3.91 (1H × 0.5, d, J = 5.1 Hz), 3.92 (1H × 0.5, d, J = 5.1 Hz), 4.41 (1H, dd, J = 9.0, 4.5 Hz), 4.52 (1H, dd, J = 9.0, 4.5 Hz), 4.82 (1H, t, J = 9.0 Hz), 7.03 (2H, d, J = 7.8 Hz), 7.12 (2H, d, J = 7.8 Hz), 7.36 (1H × 0.5, br s), 7.47 (1H ×

0.5, br s).

[0317]

Example 20

N-(7-Formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-
5 1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of N-(3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (650 mg, 1.71 mmol) obtained in Example 3 and 1,1-dichloromethyl methyl ether (237 mg, 2.06 mmol)
10 in dichloromethane (5 mL) was added dropwise at 0°C under an argon atmosphere and ice-cooling titanium tetrachloride (0.34 mL, 3.07 mmol), and the mixture was stirred at the same temperature for 20 minutes. Water was added to the reaction solution and the product was extracted with
15 dichloromethane. The organic layer was washed with an aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate =
20 4 : 1) to obtain 520 mg (yield: 75%) of the title compound. Melting point: 177 - 178°C.

¹H-NMR (CDCl₃) δ: 1.11 (9H, s), 1.22 (6H, d, J = 6.9 Hz), 1.91 (3H, s), 2.26 (2H, s), 2.51 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 4.49-4.61 (2H, m), 4.92-5.05 (1H, m), 6.55 (1H,
25 br s), 7.03 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz),

10.4 (1H, s).

[0318]

Example 21

N-(7-(Hydroxymethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-
5 2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of N-(7-formyl-3-(4-isopropylphenyl)-
4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-
dimethylbutanamide (370 mg, 0.91 mmol) obtained in Example
20 in methanol (5 mL) was added sodium borohydride (34 mg,
10 0.91 mmol) at room temperature and the mixture was stirred
for 1 hour. The reaction solution was concentrated under
reduced pressure and the residue was extracted with ethyl
acetate. The organic layer was washed with water, dried
over anhydrous sodium sulfate, and concentrated under
15 reduced pressure. The obtained residue was recrystallized
from ethyl acetate - hexane to obtain 290 mg (yield: 78%)
of the title compound. Melting point: 274 - 275°C.

¹H-NMR (CDCl₃) δ: 1.12 (9H, s), 1.22 (6H, d, J = 6.9 Hz),
1.86 (3H, s), 2.00 (1H, br s), 2.26 (5H, s), 2.86 (1H,
20 septet, J = 6.9 Hz), 4.43 (1H, dd, J = 8.1, 4.8 Hz), 4.52
(1H, dd, J = 9.3, 4.8 Hz), 4.64-4.93 (3H, m), 6.54 (1H, br
s), 7.03 (2H, d, J = 8.1 Hz), 7.11 (2H, d, J = 8.1 Hz).

[0319]

Example 22

25 N-(7-(1-Hydroxyethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-

2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To methylmagnesium bromide (2.0 M THF solution, 5.0 mL, 10.0 mmol) was added N-(7-formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-

5 dimethylbutanamide (780 mg, 1.91 mmol) obtained in Example 20 at 0°C and the reaction solution was stirred at the same temperature for 1 hour. The reaction solution was added to water and the product was extracted with ethyl acetate.

The organic layer was washed with water and saturated brine, 10 dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was recrystallized from hexane - ethyl acetate to obtain 590 mg (yield: 73%) of the title compound as a diastereomer mixture. Melting point: 156 - 157°C (ethyl acetate - hexane).

15 ¹H-NMR (CDCl₃) δ: 0.87-1.32 (15H, m), 1.50-1.62 (3H, m), 1.86 (3H, s), 2.17-2.25 (5H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.42-3.52 (1H, m), 4.47-4.52 (2H, m), 4.82-5.09 (2H, m), 6.50 (1H, br s), 7.00-7.05 (2H, m), 7.03-7.15 (2H, m).

[0320]

20 Example 23

N-(7-Ethyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a mixture of N-(7-(1-hydroxyethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (200 mg, 0.47 mmol) obtained in 25

Example 22 and trifluoroacetic acid (3 mL) was added under ice cooling triethylsilane (0.5 mL, 3.2 mmol) and the resulting mixture was stirred at room temperature for 30 minutes. After the reaction solution was concentrated under reduced pressure, to the residue was added an aqueous saturated sodium hydrogen carbonate solution and the aqueous layer was made alkaline, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) and recrystallized from hexane to obtain 100 mg (yield: 52%) of the title compound. Melting point: 135 - 136°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.90-1.25 (18H, m), 1.84 (3H, s), 2.18 (3H, s), 2.24 (2H, s), 2.65 (2H, q, $J = 7.5$ Hz), 2.85 (1H, septet, $J = 6.9$ Hz), 4.40 (1H, dd, $J = 8.7, 4.8$ Hz), 4.50 (1H, dd, $J = 9.0, 4.8$ Hz), 4.81 (1H, t, $J = 9.0$ Hz), 6.50 (1H, br s), 7.03 (2H, d, $J = 8.1$ Hz), 7.11 (2H, d, $J = 8.1$ Hz).

[0321]

Example 24

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-N,3,3-trimethylbutanamide

To a solution of N-(3-(4-isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (200 mg, 0.51 mmol) synthesized in Example 1 in DMF (3 mL) was added sodium hydride (a 60% dispersion in liquid paraffin, 24 mg, 0.6 mmol) at 0°C and the resulting mixture was stirred at room temperature for 30 minutes. To the reaction solution was added methyl iodide (78 mg, 0.55 mmol) and the resulting mixture was stirred at room temperature for 30 minutes. Water was added to the reaction solution and the product was extracted with diisopropyl ether. The extracts were washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 25 mg (yield: 12%) of the desired product having low polarity, of two rotational isomers of the title compound. Melting point: 122 - 123°C (petroleum ether).

¹H-NMR (CDCl₃) δ: 0.99 (9H, s), 1.23 (6H, d, J = 6.9 Hz), 1.75 (3H, s), 1.79 (2H, s), 2.06 (3H, s), 2.18 (3H, s), 2.87 (1H, septet, J = 6.9 Hz), 3.00 (3H, s), 4.44 (1H, dd, J = 8.7, 4.8 Hz), 4.55 (1H, dd, J = 9.0, 4.8 Hz), 4.87 (1H, t, J = 9.0 Hz), 7.02 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz).

Example 25

N-(3-(4-Isopropylphenyl)-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-5-yl)-N,3,3-trimethylbutanamide

By the silica gel column chromatography (hexane : ethyl acetate = 4 : 1) in Example 24, 28 mg (yield: 14%) of the title compound having high polarity of the two rotational isomers was obtained. Melting point: 80 - 82°C (petroleum ether).

¹H-NMR (CDCl₃) δ: 0.91 (9H, s), 1.21 (6H, d, J = 6.9 Hz), 1.72 (2H, s), 1.73 (3H, s), 2.07 (3H, s), 2.19 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.06 (3H, s), 4.43 (1H, dd, J = 8.7, 4.8 Hz), 4.55 (1H, dd, J = 9.0, 4.8 Hz), 4.86 (1H, t, J = 9.0 Hz), 6.95 (2H, d, J = 8.1 Hz), 7.11 (2H, d, J = 8.1 Hz).

[0323]

Example 26

N-(3-(4-Isopropylphenyl)-4,6-dimethyl-7-(1-pyrrolidinylmethyl)-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of pyrrolidine (0.20 mL, 2.4 mmol) in methanol (5 mL) was added titanium tetraisopropoxide (0.36 mL, 1.20 mmol) and N-(7-formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (250 mg, 0.61 mmol) obtained in Example 20 at 0°C and the resulting mixture was stirred at room

temperature for 14 hours. To the reaction solution was added sodium borohydride (23.2 mg, 0.61 mol) at room temperature and the resulting mixture was stirred for 1.5 hours. Water was added to the reaction solution and the product was concentrated under reduced pressure, and the residue was extracted with ethyl acetate. The obtained residue was purified by basic silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 140 mg (yield: 49%) of the title compound. Amorphous substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.09 (9H, s), 1.21 (6H, d, $J = 6.9$ Hz), 1.62-1.87 (7H, m), 2.22 (2H, s), 2.26 (3H, s), 2.47-2.62 (4H, m), 2.85 (1H, septet, $J = 6.9$ Hz), 3.58 (1H, d, $J = 12.0$ Hz), 3.67 (1H, d, $J = 12.0$ Hz), 4.38 (1H, dd, $J = 8.4$, 4.5 Hz), 4.48 (1H, dd, $J = 9.0$, 4.5 Hz), 4.78 (1H, t, $J = 9.0$ Hz), 6.65 (1H, br s), 7.01 (2H, d, $J = 8.1$ Hz), 7.10 (2H, d, $J = 8.1$ Hz).

[0324]

Example 27

N-(7-((Dimethylamino)methyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using N-(7-formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

obtained in Example 20, the title compound was synthesized

in the same manner as in Example 26. Yield: 37%.

Amorphous substance.

¹H-NMR (CDCl₃) δ: 1.11 (9H, s), 1.21 (6H, d, J = 6.9 Hz),
1.85 (3H, s), 2.20-2.32 (11H, m), 2.85 (1H, septet, J = 6.9
5 Hz), 3.39 (1H, d, J = 12.3 Hz) , 3.45 (1H, d, J = 12.3 Hz),
4.40 (1H, dd, J = 8.7, 4.8 Hz), 4.51 (1H, dd, J = 9.0, 4.8
Hz), 4.80 (1H, t, J = 8.7 Hz), 6.51 (1H, br s), 7.01 (2H, d,
J = 8.1 Hz), 7.10 (2H, d, J = 8.1 Hz).

[0325]

10 Example 28

N-(7-(1-Hydroxyethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-
2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To methylmagnesium bromide (2.0 M THF solution, 5.0 mL,
10.0 mmol) was added N-(7-formyl-3-(4-isopropylphenyl)-4,6-
15 dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-
dimethylbutanamide (1.0 g, 1.91 mmol) obtained in Example
20 at 0°C and the reaction solution was stirred at the same
temperature for 1 hour. The reaction solution was poured
into water and the product was extracted with ethyl acetate.
20 The organic layer was washed with water and 1 N
hydrochloric acid, dried over anhydrous sodium sulfate, and
concentrated under reduced pressure. The obtained residue
was purified by silica gel column chromatography (hexane :
ethyl acetate = 4 : 1) to obtain 192 mg (yield: 19%) of the
25 title compound as a low polarity isomer. Melting point:

147 - 148°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 1.12 (9H, s), 1.21 (6H, d, J = 6.9 Hz),
1.51 (3H, d, J = 6.6 Hz), 1.86 (3H, s), 2.17 (3H, s), 2.25
(2H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.51 (1H, d, J =
5 10.5 Hz), 4.43-4.58 (2H, m), 4.82-5.11 (2H, m), 6.51 (1H,
br s), 7.02 (2H, d, J = 8.1 Hz), 7.11 (2H, d, J = 8.1 Hz).

[0326]

Example 29

N-(7-(1-Hydroxyethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-
10 2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

The residue treated in the same manner as described in
the Example 28 was purified by silica gel column
chromatography (hexane : ethyl acetate = 4 : 1) to obtain
122 mg (yield: 12%) of the title compound as a high
15 polarity isomer. Melting point: 169 - 170°C (ethyl acetate
- hexane).

¹H-NMR (CDCl₃) δ: 1.12 (9H, s), 1.22 (6H, d, J = 6.9 Hz),
1.55 (3H, d, J = 6.6 Hz), 1.85 (3H, s), 2.18 (3H, s), 2.25
(2H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.49 (1H, d, J =
20 9.9 Hz), 4.43-4.58 (2H, m), 4.82-5.12 (2H, m), 6.53 (1H, br
s), 7.03 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz).

[0327]

Example 30

N-(7-(1-Hydroxypropyl)-3-(4-isopropylphenyl)-4,6-dimethyl-
25 2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To ethylmagnesium chloride (2.0 M THF solution , 5.0 mL, 10.0 mmol) was added N-(7-formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (0.7 g, 1.72 mmol) obtained in Example 20 at 0°C and the reaction solution was stirred at the same temperature for 1 hour. The reaction solution was added to water and the product was extracted with ethyl acetate. The organic layer was washed with water and 1 N hydrochloric acid, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 264 mg (yield: 35%) of the title compound as a low polarity isomer. Melting point: 145 - 146°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.90-1.05 (3H, m), 1.11 (9H, s), 1.21 (6H, d, J = 6.9 Hz), 1.69-1.95 (5H, m), 2.17 (3H, s), 2.25 (2H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.32 (1H, d, J = 10.2 Hz), 4.41-4.57 (2H, m), 4.72-4.90 (2H, m), 6.51 (1H, br s), 7.01 (2H, d, J = 8.1 Hz), 7.11 (2H, d, J = 8.4 Hz).

[0328]

Example 31

N-(7-(1-Hydroxypropyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

The residue treated in the same manner as described in the Example 30 was purified by silica gel column

chromatography (hexane : ethyl acetate = 4 : 1) to obtain 160 mg (yield: 21%) of the title compound as a high polarity isomer. Melting point: 165 - 167°C (ethyl acetate - hexane).

5 $^1\text{H-NMR}$ (CDCl_3) δ : 0.87-1.09 (3H, m), 1.11 (9H, s), 1.22 (6H, d, $J = 6.9$ Hz), 1.77-1.93 (5H, m), 2.17 (3H, s), 2.24 (2H, s), 2.86 (1H, septet, $J = 6.9$ Hz), 3.36 (1H, d, $J = 10.2$ Hz), 4.40-4.52 (2H, m), 4.72-4.90 (2H, m), 6.56 (1H, br s), 7.01 (2H, d, $J = 8.4$ Hz), 7.12 (2H, d, $J = 8.4$ Hz).

10 [0329]

Example 32

N-(7-Acetyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

A mixture of N-(7-(1-hydroxyethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (580 mg, 1.37 mmol) obtained in Example 22 and manganese dioxide (1.43 g, 16.4 mmol) were stirred at 100°C for two hours. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 440 mg (yield: 76%) of the title compound. Melting point: 200 - 201°C (ethyl acetate - hexane).

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.12 (9H, s), 1.22 (6H, d, $J = 6.8$ Hz), 1.89 (3H, s), 2.23 (3H, s), 2.26 (2H, s), 2.58 (3H, s),

2.87 (1H, septet, $J = 6.8$ Hz), 4.41-4.58 (2H, m), 4.78-4.96 (1H, m), 6.47 (1H, br s), 7.03 (2H, d, $J = 8.2$ Hz), 7.14 (2H, d, $J = 8.2$ Hz).

[0330]

5 Example 33

N-(7-(1-Hydroxy-1-methylethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

10 Using N-(7-acetyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Example 32, the title compound was synthesized in the same manner as in Example 22. Yield: 34%. Melting point: 133 - 134°C (ethyl acetate - hexane).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.12 (9H, s), 1.21 (6H, d, $J = 6.8$ Hz), 1.68 (3H, s), 1.70 (3H, s), 1.86 (3H, s), 2.26 (2H, s), 2.35 (3H, s), 2.86 (1H, septet, $J = 6.8$ Hz), 4.37-4.55 (3H, m), 4.75-4.88 (1H, m), 6.47 (1H, br s), 7.03 (2H, d, $J = 8.2$ Hz), 7.13 (2H, d, $J = 8.2$ Hz).

[0331]

20 Example 34

N-(3-(4-Isopropylphenyl)-4,6-dimethyl-7-propyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

25 Using a diastereo mixture of N-(7-(1-hydroxypropyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in the synthesis in

Examples 30 and 31, the title compound was synthesized in the same manner as in Example 23. Yield: 86%. Melting point: 145 - 148°C (ethyl acetate - hexane).

¹H-NMR (CDCl₃) δ: 0.80-1.35 (18H, m), 1.45-1.65 (2H, m),
5 1.80 (3H, s), 2.17 (3H, s), 2.25 (2H, s), 2.57-2.68 (2H, m),
2.85 (1H, septet, J = 6.8 Hz), 4.40 (1H, dd, J = 8.4, 6.6
Hz), 4.50 (1H, dd, J = 8.8, 6.6 Hz), 4.80 (1H, t, J = 8.4
Hz), 6.49 (1H, br s), 7.04 (2H, d, J = 8.4 Hz), 7.12 (2H, d,
J = 8.4 Hz).

10 [0332]

Example 35

N-(7-Bromo-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-
1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of N-(3-(4-isopropylphenyl)-4,6-
15 dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-
dimethylbutanamide (1.0 g, 2.63 mmol) obtained in Example 3
in acetonitrile (30 mL) was added N-bromosuccinimide (468
mg, 2.63 mmol) at 0°C and the reaction mixture was stirred
at room temperature for 2 hours. Water was added to the
20 reaction solution, the organic layer was separated, and the
aqueous layer was extracted with ethyl acetate. The
combined organic layers were washed with water, dried over
magnesium sulfate, filtered, and concentrated under reduced
pressure. The solvent was distilled off under reduced
25 pressure. The obtained residue was recrystallized from

ethanol to obtain 1.10 g (yield: 91%) of the title compound.
Melting point: 191 - 193°C.

¹H-NMR (CDCl₃) δ: 1.11 (9H, s), 1.22 (6H, d, J = 6.9 Hz),
1.82 (3H, s), 2.24 (2H, s), 2.33 (3H, s), 2.86 (1H, septet,
5 J = 6.9 Hz), 4.51 (1H, dd, J = 9.0, 4.8 Hz), 4.63 (1H, dd,
J = 9.0, 4.8 Hz), 4.93 (1H, t, J = 9.3 Hz), 6.54 (1H, br s),
7.03 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J = 8.1 Hz).

[0333]

Example 36

10 N-(3-(4-Isopropylphenyl)-7-methoxy-4,6-dimethyl-2,3-
dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

A mixture of N-(7-bromo-3-(4-isopropylphenyl)-4,6-
dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-
dimethylbutanamide (250 mg, 0.545 mmol) obtained in Example
15 35, copper(I) bromide (78 mg, 0.545 mmol), ethyl acetate
(88 mg, 1.00 mmol), and 28% sodium methoxide-methanol
solution (20 mL) was refluxed with heating for 6 hours. 1
N Hydrochloric acid was added to the reaction solution and
the product was extracted with diisopropyl ether. The
20 extracts were washed with water, dried over magnesium
sulfate, filtered, and concentrated under reduced pressure.
The obtained residue was purified by silica gel column
chromatography (hexane : ethyl acetate = 4 : 1) and
recrystallized from hexane - ethyl acetate to obtain 130 mg
25 (yield: 58%) of the title compound. Melting point: 191 -

193°C.

¹H-NMR (CDCl₃) δ: 1.11 (9H, s), 1.22 (6H, d, J = 6.9 Hz),
1.83 (3H, s), 2.16 (3H, s), 2.25 (2H, s), 2.86 (1H, septet,
J = 6.9 Hz), 3.89 (3H, s), 4.44-4.55 (2H, m), 4.87 (1H, t,
5 J = 8.1 Hz), 6.47 (1H, br s), 7.05 (2H, d, J = 8.1 Hz),
7.13 (2H, d, J = 8.1 Hz).

[0334]

Example 37

(+)-N-((3R)-3-(4-Isopropylphenyl)-4,6-dimethyl-2,3-dihydro-
10 1-benzofuran-5-yl)-3,3-dimethylbutanamide

Using (+)-(3R)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-
dihydro-1-benzofuran-5-amine obtained in Reference Example
242, the title compound was synthesized in the same manner
as in Example 1. Yield: 93%. Melting point: 148 - 149°C
15 (ethyl acetate - hexane). $[\alpha]_D^{20} = + 93.2^\circ$ (c = 0.54,
chloroform).

¹H-NMR (CDCl₃) δ: 1.11 (9H, s), 1.22 (6H, d, J = 6.9 Hz),
1.86 (3H, s), 2.22 (3H, s), 2.24 (2H, s), 2.86 (1H, septet,
J = 6.9 Hz), 4.41 (1H, dd, J = 9.0, 4.8 Hz), 4.50 (1H, dd,
20 J = 9.0, 4.8 Hz), 4.83 (1H, t, J = 9.0 Hz), 6.47 (1H, br s),
6.63 (1H, s), 7.04 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J =
8.1 Hz).

[0335]

Example 38

25 (+)-N-((3R)-7-Acetyl-3-(4-isopropylphenyl)-4,6-dimethyl-

2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

To a solution of (+)-N-((3R)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (933 mg, 2.46 mmol) obtained in Example 5 37 in dichloromethane (20 mL) was added aluminum chloride (721 mg, 5.40 mmol) at -70°C under an argon atmosphere and the mixture was stirred for 20 minutes. To the reaction solution was added dropwise acetyl chloride (424 mg, 5.40 mmol) at the same temperature and the reaction mixture was 10 gradually warmed to 10°C. The reaction solution was added to ice, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, an aqueous saturated sodium hydrogen carbonate solution and saturated brine, 15 dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to synthesize 873 mg (yield: 84%) of the title compound. Melting point: 176 - 177°C (ethyl acetate - 20 hexane). $[\alpha]_D^{20} = + 6.2^\circ$ (c = 0.53, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (9H, s), 1.22 (6H, d, J = 6.9 Hz), 1.88 (3H, s), 2.22 (3H, s), 2.25 (2H, s), 2.58 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 4.46-4.55 (2H, m), 4.89 (1H, t, J = 8.4 Hz), 6.53 (1H, br s), 7.03 (2H, d, J = 8.1 Hz), 25 7.14 (2H, d, J = 8.1 Hz).

[0336]

Example 39

(-)-N-((3R)-7-Formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

5 Using (+)-N-((3R)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Example 37, the title compound was synthesized in the same manner as in Example 20. Yield: 83%. Melting point: 179 - 180°C (ethyl acetate - hexane). $[\alpha]_D^{20} = -$
 10 25.8° (c = 0.48, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.12 (9H, s), 1.22 (6H, d, J = 6.9 Hz), 1.92 (3H, s), 2.23 (2H, s), 2.52 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 4.45-4.60 (2H, m), 4.97 (1H, t, J = 10.8 Hz), 6.49 (1H, br s), 7.03 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J =
 15 8.1 Hz), 10.43 (1H, s).

[0337]

Example 40

(+)-N-((3R)-7-(1-Hydroxyethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide
 20 dimethylbutanamide

A compound, which was produced according to the same manner as in Example 22 using (-)-N-((3R)-7-formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Example 39, was
 25 purified by silica gel column chromatography (hexane :

ethyl acetate = 4 : 1) to obtain a low polarity isomer of the title compound. Yield: 33%. Melting point: 188 - 189°C (ethyl acetate - hexane). $[\alpha]_D^{20} = + 63.4^\circ$ (c = 0.49, chloroform).

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (9H, s), 1.22 (6H, d, J = 6.9 Hz), 1.52 (3H, d, J = 6.6 Hz), 1.85 (3H, s), 2.18 (3H, s), 2.25 (2H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.50 (1H, br d), 4.45-4.54 (2H, m), 4.85-4.94 (1H, m), 5.00-5.10 (1H, m), 6.50 (1H, br s), 7.02 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J =
10 8.1 Hz).

[0338]

Example 41

(+)-N-((3R)-7-(1-Hydroxyethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide
15

A compound, which was produced according to the same manner as in Example 22 using (-)-N-((3R)-7-formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Example 39, was
20 purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain a high polarity isomer of the title compound. Yield: 49%. Melting point: 149 - 150°C (ethyl acetate - hexane). $[\alpha]_D^{20} = + 15.2^\circ$ (c = 0.49, chloroform).

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.12 (9H, s), 1.22 (6H, d, J = 6.9 Hz),

1.55 (3H, d, J = 6.6 Hz), 1.85 (3H, s), 2.19 (3H, s), 2.25
 (2H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.47 (1H, br d),
 4.40-4.55 (2H, m), 4.83-4.91 (1H, m), 5.01-5.11 (1H, m),
 6.50 (1H, br s), 7.03 (2H, d, J = 7.8 Hz), 7.13 (2H, d, J =
 5 7.8 Hz).

[0339]

Example 42

(+)-N-((3R)-7-Ethyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-
 dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

10 A solution of (+)-N-((3R)-7-(1-hydroxyethyl)-3-(4-
 isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-
 yl)-3,3-dimethylbutanamide (746 mg, 1.77 mmol) obtained in
 Examples 40 and 41, and 10% palladium on carbon (water
 content: 50%, 75 mg) in ethanol (8 mL) was refluxed with
 15 heating for 2 hours. The catalyst was removed and the
 reaction solution was concentrated under reduced pressure.
 The obtained residue was recrystallized from THF - hexane
 to obtain 589 mg (yield: 96%) of the title compound.
 Melting point: 156 - 157°C. $[\alpha]_D^{20} = + 50.7^\circ$ (c = 0.46,
 20 chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.12 (9H, s), 1.14 (3H, t, J = 7.5 Hz),
 1.22 (6H, d, J = 6.9 Hz), 1.85 (3H, s), 2.18 (3H, s), 2.25
 (2H, s), 2.66 (2H, q, J = 7.5 Hz), 2.85 (1H, septet, J =
 6.9 Hz), 4.41 (1H, dd, J = 9.0, 4.5 Hz), 4.51 (1H, dd, J =
 25 9.0, 4.5 Hz), 4.82 (1H, t, J = 9.0 Hz), 6.47 (1H, br s),

7.04 (2H, d, J = 7.8 Hz), 7.12 (2H, d, J = 7.8 Hz).

[0340]

Example 43

(+)-N-((3R)-7-(1-Hydroxypropyl)-3-(4-isopropylphenyl)-4,6-
5 dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-
dimethylbutanamide

A compound, which was produced according to the same
manner as in Example 30 using (-)-N-((3R)-7-formyl-3-(4-
isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-
10 yl)-3,3-dimethylbutanamide obtained in Example 39, was
purified by silica gel column chromatography (hexane :
ethyl acetate = 4 : 1) to obtain a low polarity isomer of
the title compound. Yield: 25%. Melting point: 205 -
206°C (ethyl acetate - hexane). $[\alpha]_D^{20} = + 54.8^\circ$ (c = 0.44,
15 chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.99 (3H, t, J = 7.5 Hz), 1.11 (9H, s),
1.21 (6H, d, J = 6.9 Hz), 1.70-1.93 (5H, m), 2.17 (3H, s),
2.23 (2H, s), 2.86 (1H, septet, J = 6.9 Hz), 3.31 (1H, br
d), 4.42-4.52 (2H, m), 4.74-4.80 (1H, m), 4.85 (1H, t, J =
20 8.1 Hz), 6.49 (1H, br s), 7.01 (2H, d, J = 8.4 Hz), 7.11
(2H, d, J = 8.4 Hz).

[0341]

Example 44

(+)-N-((3R)-7-(1-Hydroxypropyl)-3-(4-isopropylphenyl)-4,6-
25 dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-

dimethylbutanamide

A compound, which was produced according to the same manner as in Example 30 using (-)-N-((3R)-7-formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Example 39, was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain a high polarity isomer of the title compound. Yield: 38%. Amorphous powder. $[\alpha]_D^{20} = +16.1^\circ$ (c = 0.54, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.00 (3H, t, J = 7.5 Hz), 1.09 (9H, s), 1.24 (6H, d, J = 6.9 Hz), 1.76-1.95 (5H, m), 2.15 (3H, s), 2.23 (2H, s), 2.85 (1H, septet, J = 6.9 Hz), 3.41 (1H, br d), 4.41-4.49 (2H, m), 4.73-4.88 (2H, m), 6.85 (1H, br s), 7.02 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz).

[0342]

Example 45

(+)-N-((3R)-3-(4-Isopropylphenyl)-4,6-dimethyl-7-propyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

A solution of (+)-N-((3R)-7-(1-hydroxypropyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide (620 mg, 1.42 mmol) obtained in Examples 43 and 44, and 10% palladium on carbon (water content: 50%, 62 mg) in acetic acid (3 mL) was reacted at 80°C for 2 hours. The catalyst was removed, water was added to the reaction solution, and the product was

extracted with ethyl acetate. The organic layer was washed with water, an aqueous saturated sodium hydrogen carbonate solution and saturated brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure.

5 The obtained residue was recrystallized from ethyl acetate - hexane to obtain 423 mg (yield: 71%) of the title compound. Melting point: 184 - 185°C. $[\alpha]_D^{20} = + 41.6^\circ$ (c = 0.51, chloroform).

¹H-NMR (CDCl₃) δ: 0.98 (3H, t, J = 7.5 Hz), 1.12 (9H, s),
10 1.22 (6H, d, J = 6.9 Hz), 1.50-1.60 (2H, m), 1.85 (3H, s),
2.17 (3H, s), 2.25 (2H, s), 2.57-2.63 (2H, m), 2.85 (1H, septet, J = 6.9 Hz), 4.40 (1H, dd, J = 9.0, 4.5 Hz), 4.50 (1H, dd, J = 9.0, 4.5 Hz), 4.80 (1H, t, J = 9.0 Hz), 6.46 (1H, br s), 7.04 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J = 8.1
15 Hz).

[0343]

Example 46

(+)-N-((3R)-7-(1-Hydroxy-1-methylethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide
20

Using (+)-N-((3R)-7-acetyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide obtained in Example 38, the title compound was synthesized in the same manner as in Example
25 22. Yield: 82%. Melting point: 141 - 142°C (ethyl acetate

- hexane). $[\alpha]_D^{20} = + 40.8^\circ$ ($c = 0.46$, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (9H, s), 1.22 (6H, d, $J = 6.9$ Hz),
1.68 (3H, s), 1.70 (3H, s), 1.86 (3H, s), 2.25 (2H, s),
2.35 (3H, s), 2.86 (1H, septet, $J = 6.9$ Hz), 4.37 (1H, s),
5 4.37-4.50 (2H, m), 4.75-4.87 (1H, m), 6.52 (1H, br s), 7.03
(2H, d, $J = 8.0$ Hz), 7.13 (2H, d, $J = 8.0$ Hz).

[0344]

Example 47

(+)-N-(tert-Butyl)-N'-((3R)-3-(4-isopropylphenyl)-4,6-
10 dimethyl-2,3-dihydro-1-benzofuran-5-yl)urea

To a solution of (+)-(3R)-3-(4-isopropylphenyl)-4,6-
dimethyl-2,3-dihydro-1-benzofuran-5-amine (1.0 g, 3.55
mmol) obtained in Reference Example 242 in THF (10 mL) was
added dropwise with ice-cooling 2,2,2-trichloroethyl
15 chloroformate (0.49 mL, 3.55 mmol), was added triethylamine
(0.52 mL, 3.73 mmol) and the reaction mixture was stirred
for 30 minutes, and then the reaction solution was warmed
to room temperature. Water was added to the reaction
solution, and the product was extracted with ethyl acetate.
20 The organic layer was washed with water, an aqueous
saturated sodium hydrogen carbonate solution and saturated
brine, dried over sodium sulfate, filtered, and then
concentrated under reduced pressure. The solution of the
obtained 2,2,2-trichloroethyl (3-(4-isopropylphenyl)-4,6-
25 dimethyl-2,3-dihydro-1-benzofuran-5-yl)carbamate (1.60 g,

3.50 mmol) and tert-butylamine (779 mg, 10.65 mmol) in dimethylsulfoxide (20 mL) was stirred at 45°C for 5 hours under an argon atmosphere. Water was added to the reaction solution, and the product was extracted with ethyl acetate.

5 The organic layer was washed with water, an aqueous saturated sodium hydrogen carbonate solution and saturated brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane :
10 ethyl acetate = 2 : 1) to obtain 1.19 g (yield: 88%) of the title compound. Melting point: 205 - 206°C (ethyl acetate - hexane). $[\alpha]_D^{20} = + 81.0^\circ$ (c = 0.51, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.18-1.30 (15H, m), 1.89 (3H, s), 2.25 (3H, s), 2.86 (1H, septet, J = 6.9 Hz), 4.00 (1H, br s),
15 4.45 (1H, dd, J = 8.7, 4.8 Hz), 4.53 (1H, dd, J = 8.7, 4.8 Hz), 4.88 (1H, t, J = 8.7 Hz), 5.25 (1H, br s), 6.66 (1H, s), 7.00 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 8.1 Hz).

[0345]

Example 48

20 (-)-N-(tert-Butyl)-N'-((3R)-7-formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)urea

Using (+)-N-(tert-butyl)-N'-((3R)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)urea obtained in Example 47, the title compound was
25 synthesized in the same manner as in Example 20. Yield:

78%. Melting point: 209 - 210°C (ethyl acetate - hexane).

$[\alpha]_D^{20} = -31.2^\circ$ ($c = 0.48$, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.10-1.40 (15H, m), 1.96 (3H, s), 2.57 (3H, s), 2.86 (1H, septet, $J = 6.9$ Hz), 3.97 (1H, br s),
 5 4.50-4.63 (2H, m), 4.95-5.05 (1H, m), 5.40 (1H, br s), 7.01 (2H, d, $J = 8.1$ Hz), 7.15 (2H, d, $J = 8.1$ Hz), 10.47 (1H, s).

[0346]

Example 49

10 (+)-N-(tert-Butyl)-N'-((3R)-7-(hydroxymethyl)-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)urea

Using (-)-N-(tert-butyl)-N'-((3R)-7-formyl-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-5-yl)urea obtained in Example 48, the title compound was
 15 synthesized in the same manner as in Example 21. Yield: 97%. Melting point: 187 - 188°C (ethyl acetate - hexane). $[\alpha]_D^{20} = +34.0^\circ$ ($c = 0.43$, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.12-1.28 (15H, m), 1.89 (3H, s), 2.05 (1H, br s), 2.31 (3H, s), 2.80-2.92 (1H, m), 3.99 (1H, br s), 4.48 (1H, dd, $J = 9.0, 4.5$ Hz), 4.56 (1H, dd, $J = 9.0, 4.5$ Hz); 4.72-4.82 (2H, m), 4.88 (1H, t, $J = 9.0$ Hz), 5.30 (1H, br s), 6.97 (2H, d, $J = 8.1$ Hz), 7.13 (2H, d, $J = 8.1$ Hz).

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.12-1.28 (15H, m), 1.89 (3H, s), 2.05

(1H, br s), 2.31 (3H, s), 2.86 (1H, septet, $J = 6.9$ Hz),
 3.99 (1H, br s), 4.48 (1H, dd, $J = 9.0, 4.5$ Hz), 4.56 (1H,
 dd, $J = 9.0, 4.5$ Hz), 4.72-4.82 (2H, m), 4.88 (1H, t, $J =$
 9.0 Hz), 5.30 (1H, br s), 6.97 (2H, d, $J = 8.1$ Hz), 7.13
 5 (2H, d, $J = 8.1$ Hz).

[0347]

Example 50

(+)-N-(tert-Butyl)-N'-((3R)-3-(4-isopropylphenyl)-4,6,7-
 trimethyl-2,3-dihydro-1-benzofuran-5-yl)urea

10 Using (+)-N-(tert-butyl)-N'-((3R)-7-(hydroxymethyl)-3-
 (4-isopropylphenyl)-4,6-dimethyl-2,3-dihydro-1-benzofuran-
 5-yl)urea obtained in Example 49, the title compound was
 synthesized in the same manner as in Example 45. Yield:
 57%. Melting point: 209 - 210°C (ethyl acetate - hexane).

15 $[\alpha]_D^{20} = + 53.2^\circ$ ($c = 0.47$, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.10-1.38 (15H, m), 1.87 (3H, s), 2.19
 (6H, s), 2.86 (1H, septet, $J = 6.9$ Hz), 3.99 (1H, br s),
 4.44 (1H, dd, $J = 9.0, 4.5$ Hz), 4.54 (1H, dd, $J = 9.0, 4.5$
 Hz), 4.86 (1H, t, $J = 9.0$ Hz), 5.29 (1H, br s), 6.99 (2H, d,
 20 $J = 8.1$ Hz), 7.11 (2H, d, $J = 8.1$ Hz).

[0348]

Example 51

(-)-N-((3R)-7-Bromo-3-(4-isopropylphenyl)-4,6-dimethyl-2,3-
 dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

25 Using (+)-N-((3R)-3-(4-isopropylphenyl)-4,6-dimethyl-

2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide
 obtained in Example 37, the title compound was synthesized
 in the same manner as in Example 35. Yield: 90%. Melting
 point: 118 - 119°C (ethyl acetate - hexane). $[\alpha]_D^{20} = -$
 5 13.0° (c = 0.52, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (9H, s), 1.22 (6H, d, J = 6.9 Hz),
 1.82 (3H, s), 2.24 (2H, s), 2.32 (3H, s), 2.86 (1H, septet,
 J = 6.9 Hz), 4.51 (1H, dd, J = 9.0, 4.5 Hz), 4.62 (1H, dd,
 J = 9.0, 4.5 Hz), 4.93 (1H, t, J = 9.0 Hz), 6.56 (1H, br s),
 10 7.03 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J = 8.1 Hz).

[0349]

Example 52

(+)-N-((3R)-3-(4-Isopropylphenyl)-7-methoxy-4,6-dimethyl-
 2,3-dihydro-1-benzofuran-5-yl)-3,3-dimethylbutanamide

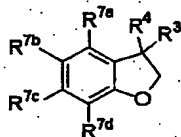
15 Using (-)-N-((3R)-7-bromo-3-(4-isopropylphenyl)-4,6-
 dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3,3-
 dimethylbutanamide obtained in Example 51, the title
 compound was synthesized in the same manner as in Example
 36. Yield: 98%. Melting point: 150 - 151°C (ethyl acetate
 20 - hexane). $[\alpha]_D^{20} = + 55.9^\circ$ (c = 0.50, chloroform).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (9H, s), 1.22 (6H, d, J = 6.9 Hz),
 1.82 (3H, s), 2.15 (3H, s), 2.24 (2H, s), 2.86 (1H, septet,
 J = 6.9 Hz), 3.88 (3H, s), 4.44-4.53 (2H, m), 4.86 (1H, t,
 J = 8.1 Hz), 6.48 (1H, br s), 7.03 (2H, d, J = 8.1 Hz),
 25 7.12 (2H, d, J = 8.1 Hz).

[0350]

The structures of the compounds of Examples are shown in the following Table 1.

[Table 1]



Example	R ³	R ⁴	R ^{7a}	R ^{7b}	R ^{7c}	R ^{7d}	comment
1	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Me	
2	H	4- <i>i</i> -PrPh	H	<i>t</i> -BuCH ₂ CONH	Me	Me	
3	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	H	
4	H	4- <i>i</i> -PrPh	H	<i>t</i> -BuCH ₂ CONH	H	H	
5	Me	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Me	
6	Me	4- <i>i</i> -PrPh	H	<i>t</i> -BuCH ₂ CONH	Me	Me	
7	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Me	(R)-(+ form
8	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Me	(S)-(- form
9	H	4- <i>i</i> -PrPh	Me	CH ₂ CH ₂ CONH	Me	Me	
10	H	4- <i>i</i> -PrPh	Me	CH ₂ (CH ₂) ₂ CONH	Me	Me	
11	H	4- <i>i</i> -PrPh	Me	CH ₂ (CH ₂) ₃ CONH	Me	Me	
12	H	4- <i>i</i> -PrPh	Me	4-MeOPhCH ₂ CONH	Me	Me	
13	H	4- <i>i</i> -PrPh	Me	4-MeOPh(CH ₂) ₂ CONH	Me	Me	
14	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuNHCONH	Me	Me	
15	H	4- <i>i</i> -PrPh	Me	EtOC(O)CONH	Me	Me	
16	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuC(O)CONH	Me	Me	
17	H	4- <i>i</i> -PrPh	Me	EtC(O)CONH	Me	Me	
18	H	4- <i>i</i> -PrPh	Me	EtCH(OH)CONH	Me	Me	
19	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH(OH)CONH	Me	Me	
20	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	CHO	
21	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	CH ₂ OH	
22	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	MeCH(OH)	
23	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Et	
24	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CON(Me)	Me	Me	less polar
25	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CON(Me)	Me	Me	more polar
26	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	CH ₂ pyrrolidine	
27	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	CH ₂ NMe ₂	
28	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	MeCH(OH)	less polar
29	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	MeCH(OH)	more polar
30	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	EtCH(OH)	less polar
31	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	EtCH(OH)	more polar
32	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Ac	
33	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Me ₂ C(OH)	
34	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	<i>n</i> -Pr	
35	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Br	
36	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	MeO	
37	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	H	(R)-(+ form
38	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Ac	(R)-(+ form
39	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	CHO	(R)-(- form
40	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	MeCH(OH)	less polar (R)-(+ form
41	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	MeCH(OH)	more polar (R)-(+ form
42	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Et	(R)-(+ form
43	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	EtCH(OH)	less polar (R)-(+ form
44	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	EtCH(OH)	more polar (R)-(+ form
45	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	<i>n</i> -Pr	(R)-(+ form
46	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Me ₂ C(OH)	(R)-(+ form
47	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuNHCONH	Me	H	(R)-(+ form
48	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuNHCONH	Me	CHO	(R)-(- form
49	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuNHCONH	Me	CH ₂ OH	(R)-(+ form
50	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuNHCONH	Me	Me	(R)-(+ form
51	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	Br	(R)-(- form
52	H	4- <i>i</i> -PrPh	Me	<i>t</i> -BuCH ₂ CONH	Me	MeO	(R)-(+ form

Formulation Example 1

The compound obtained in Example 1 was dissolved in a 30% (w/v) polyethylene glycol 400-containing saline to prepare a 0.01% solution of the compound. This solution
5 was filtered through a bacterial filter and dispensed into vials by 10 mL, to provide an injectable solution containing 1 mg of the compound in each vial.

[0351]

Formulation Example 2

10 The compound obtained in Example 1 was dissolved in a 5% cyclodextrin-containing saline to prepare a 0.1% solution of the compound. This solution was filtered through a bacterial filter and dispensed into vials by 10 mL, to provide an injectable solution containing 10 mg of
15 the compound in each vial.

[0352]

Formulation Example 3

	(1) The compound obtained in Example 1	50 mg
	(2) Lactose	34 mg
20	(3) Corn Starch	10.6 mg
	(4) Corn Starch (paste)	5 mg
	(5) Magnesium stearate	0.4 mg
	(6) Calcium carboxymethylcellulose	20 mg
	Total	120 mg
25	According to a conventional method, the above-	

mentioned (1) to (6) are mixed and compressed by a tableting machine to produce tablets.

[0353]

Experimental Example 1

5 $[^3\text{H}]$ -CP55,940 binding assay with a cell membrane fraction expressing human CB1 and CB2 receptor

$[^3\text{H}]$ -CP55940 binding inhibition assay was conducted by incubating a CHO cell membrane fraction expressing human CB1 receptor and the test compound and 500pM $[^3\text{H}]$ -CP55940
10 in reaction buffer (50 mM Tris-HCl (pH7.4), 5 mM MgCl_2 , 2.5 mM EDTA and 0.5% BSA (fatty acid free)) at room temperature for 60 minutes. The reaction solution was filtered through GF/C filter, washed with 300 μl of washing buffer (50mM Tris-HCl (pH7.4), 0.05% BSA (fatty acid free)) four times,
15 and the radioactivity of the filter was measured with a Top Count scintillation counter (Packard). As results, the test compound has inhibited binding of $[^3\text{H}]$ -CP55940 to the membrane fraction dose-dependently.

 The inhibitory activity of the test compound to $[^3\text{H}]$ -CP55940 binding was calculated by percent on the basis that
20 radioactivity is 100% when only 500pM $[^3\text{H}]$ -CP55940 was added, and 0% when 500pM $[^3\text{H}]$ -CP55940 and 100nM CP55940 were added at the same time. Further, IC_{50} value of the test compound was calculated by analyzing concentrations
25 and percents of the test compound with PRISM 3.0 (Graphpad

Software, Inc.).

The same assay was also conducted for a CHO cell membrane fraction expressing human CB2 receptor, and the inhibitory activity to [³H]-CP55940 binding was calculated.

5 [Table 2]

Compound No.	CB1 IC ₅₀ value (nM)	CB2 IC ₅₀ value (nM)
Reference Example 153	110	560
Reference Example 212	69	<10
Reference Example 230	55	55
Reference Example 233	38	47
Reference Example 234	40	31
Example 1	20	<10
Example 7	<10	<10
Example 9	79	11
Example 14	20	<10
Example 22	11	<10
Example 23	<10	<10
Example 28	<10	<10
Example 29	<10	<10
Example 31	<10	<10
Example 32	<10	<10
Example 33	14	<10
Example 34	<10	<10
Example 35	<10	<10
Example 36	<10	<10

[0354]

Experimental Example 2

Body temperature-lowering action on mouse

10 CB1 receptor agonistic activity of the compound of the present invention in vivo was evaluated by investigating the effect on the body temperature of mouse after the drug

was administered to the mouse. In this experiment, Jcl: ICR male mice (5 weeks old) were used. After measuring the rectal temperature with a thermometer (Physitemp BAT-12) that was connected to a probe for measuring body temperature, the compound dissolved in 2.2% EtOH and 5% G2- β -cyclodextrin (solvent) was administered intraperitoneally. Solvent only was administered to the control group. 30 minutes after administration, rectal temperature was measured again. The experiment was conducted for 4 subjects per a group.

The test result was estimated as effective if the compound of the present invention lowered the body temperature substantially by 1°C or more when compared with the control group 30 minutes after administration of 1 mg/kg, i.p.

[Table 3]

Compound No.	Test Results
Example 1	Effective
Example 7	Effective
Example 14	Effective
Example 22	Effective
Example 23	Effective
Example 28	Effective
Example 29	Effective
Example 31	Effective
Example 32	Effective
Example 33	Effective
Example 34	Effective
Example 35	Effective
Example 36	Effective

[0355]

As shown in Table 3, the compound of the present invention exerted unusually body temperature-lowering action based on CB1 receptor agonistic activity at the low doses.

5 [0356]

Experimental Example 3

Effects of reducing cerebral infarction in experimental model of cerebral infarction

10 In this experiment, Jcl: SD male rats (8 weeks old) were used. A canula for infusion was inserted into the left common carotid vein under halothane anesthesia. Silicon-coated embolus was inserted into the left common carotid artery, to obstruct the middle cerebral artery (MCAO). 120 minutes after the obstruction, light
15 anesthesia was conducted again with halothane, and reperfusion was done with the embolus removed. During MCAO, the rats were observed for neural symptoms. The rats expressing typical neural symptoms were used in the experiment. The drug was dissolved in 2.2% EtOH and 5% G2-
20 β -cyclodextrin (solvent). The test compound was administered intraperitoneally at three times as much as the minimum dose which was recognized to have body temperature lowering action immediately after the reperfusion, and further administered after 2, 4 and 6
25 hours at the same dose. The same amount of the solvent was

administered to the control group. 2 days after treating MCAO, the rats were decapitated, the brain was extracted and 6 frontal slices of 2 mm thickness was constructed under ice-cooling. Each slice was dyed with a 1% TTC solution at 37°C for 15 minutes, and photographed with a digital camera. White-part area of each slice was measured by image analyzing software (Photoshop (trademark)), and the volume of the infarction was calculated by multiplying the area by the thickness of the slice.

10 [0357]

As shown above, Compound (I), etc. have excellent modulating action on cannabinoid receptor function. Further, Compound (I), etc. have protective action on cerebral infarction, and, therefore, have medical actions such as treating cerebrovascular disorders. Further, Compound (I), etc. are considered to have very low toxicity and be well transferred into the brain.

[0358]

[Effects of the Invention]

20 As described above, an excellent cannabinoid receptor modulator is provided according to the present invention.